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**Medical cannabis versus opioids for chronic noncancer pain:
A systematic review and network meta-analysis of
randomized clinical trials**

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Medical cannabis versus opioids for chronic noncancer pain: A systematic review and network meta-analysis of randomized clinical trials

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ABSTRACT**OBJECTIVE**

To evaluate the comparative benefits and harms of opioids and medical cannabis for chronic noncancer pain.

DESIGN

Systematic review and network meta-analysis.

DATA SOURCES

EMBASE, MEDLINE, CINAHL, AMED, PsycINFO, PubMed, Web of Science, Cannabis-Med, Epistemonikos and the Cochrane Library (CENTRAL).

STUDY SELECTION

Randomized trials comparing medical cannabis or opioids, against each other or placebo, with patient follow-up ≥ 4 weeks.

DATA EXTRACTION AND SYNTHESIS

Paired reviewers independently extracted data. We used Bayesian random-effects network meta-analyses to summarize the evidence and the GRADE approach to evaluate the certainty of evidence and communicate our findings.

RESULTS

Ninety trials involving 22 028 patients were eligible for review, among which the length of follow-up ranged from 28 to 180 days. Moderate certainty evidence showed that opioids provide small improvements in pain, physical functioning, and sleep quality vs. placebo; low to moderate certainty evidence supported similar effects for medical cannabis vs. placebo. Neither were more effective than placebo for role, social or emotional functioning (all high to moderate certainty evidence). Moderate certainty evidence showed there is probably little to no difference between

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3 medical cannabis and opioids for physical functioning (weighted mean difference [WMD] 0.47
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5 on the 100-point SF-36 physical component summary score, 95% CrI -1.97 to 2.99), and
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7 cannabis resulted in fewer discontinuations due to adverse events vs. opioids (odds ratio 0.55,
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9 95% CrI 0.36 to 0.83). Low certainty evidence suggested little to no difference between medical
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11 cannabis and opioids for pain relief (WMD 0.23cm on a 10cm visual analogue scale [VAS], 95%
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13 CrI -0.06 to 0.53) or sleep quality (WMD 0.49mm on a 100mm VAS, 95% CrI -4.72 to 5.59).

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15 **CONCLUSIONS**
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17 Medical cannabis may be similarly effective and less harmful than opioids for chronic noncancer
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19 pain.
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23 **PROSPERO registration number**
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25 CRD42020185184
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32 Word count: 286
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WHAT IS ALREADY KNOWN ON THIS TOPIC

There is increasing interest in medical cannabis as a therapeutic alternative to opioids for the treatment of chronic noncancer pain. The use of cannabis for chronic pain, however, is controversial, and clinical practice guidelines from the National Institute for Health and Care Excellence (NICE) and the International Association for the Study of Pain (ISAP) have made strong recommendations against use. The comparative effectiveness of cannabis versus opioids for chronic pain is uncertain.

WHAT THIS STUDY ADS

This network meta-analysis that included 90 randomized trials of 22 028 participants with chronic noncancer pain found that both opioids and medical cannabis were associated with small improvements in pain, physical function, and sleep quality compared with placebo. Medical cannabis was similarly effective to opioids and resulted in fewer discontinuations due to adverse events.

Introduction

Chronic noncancer pain impacts 20% of the global population and is associated with reduced quality of life, disability, and considerable socioeconomic burden.¹⁻⁴ Opioids are commonly prescribed for chronic noncancer pain and may provide improvement in pain relief, physical functioning and quality of sleep compared to placebo;⁵ however, they are also associated with harms including addiction, overdose and death.^{6,7} There is growing interest in cannabis as an alternative to long-term opioid use,⁸ and countries increasingly permit therapeutic use of cannabis.⁹ Two-thirds of medical cannabis users endorse management of chronic pain as their indication for use.¹⁰ Despite increasing availability of medical cannabis its' use for chronic pain remains controversial due, in part, to conflicting recommendations. A 2019 guideline from the National Institute for Health and Care Excellence (NICE) made strong recommendations against use of cannabis for chronic pain, and in 2021 the International Association for the Study of Pain (IASP) released a position statement against the use of cannabinoids for pain.^{11,12} Alternately, a 2021 BMJ Rapid Recommendation made a conditional recommendation to offer a trial of non-inhaled medical cannabis for people living with chronic pain if standard care was insufficient.¹³ We undertook a systematic review and network meta-analysis of randomized controlled trials (RCTs) to explore the comparative benefits and harms of medical cannabis and opioids for chronic noncancer pain.

Methods

We adhered to the Preferred Reporting items for Systematic reviews and Meta-Analyses extension statement for network meta-analysis (PRISMA-NMA),¹⁴ registered our review on PROSPERO (CRD42020185184),¹⁵ and followed GRADE guidance for communicating our findings.¹⁶

Data Sources and Searches

We searched EMBASE, MEDLINE, CINAHL, AMED, PsycINFO, PubMed, Web of Science, Cannabis-Med, Epistemonikos and the Cochrane Library (CENTRAL) from inception to March 2021, without language restrictions. An experienced medical librarian developed database-specific search strategies (eAppendix 1 in Supplement). We reviewed reference lists of eligible studies, and relevant reviews and guidelines, to identify additional studies. We included RCTs that enrolled ≥ 20 patients with chronic noncancer pain (pain lasting ≥ 3 months), randomized them to any type of cannabis for therapeutic use, an opioid, or placebo and followed them for ≥ 4 weeks to allow for sufficient time for functional outcomes to manifest among treatment responders.¹³ Trials including patients with chronic cancer and noncancer pain were included if outcome data were reported separately. We excluded conference abstracts and trials of combination products (e.g., opioids with nonsteroidal anti-inflammatory drugs or anti-depressants).

Pairs of reviewers independently screened titles and abstracts, and full text reports, and extracted data using standardized, pilot-tested forms using online systematic review software (DistillerSR, Evidence Partners, Ottawa, Canada; <http://systematic-review.net/>). For all eligible trials, we collected information regarding study characteristics, intervention details, patient characteristics,

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3 and all patient-important outcomes as guided by the Initiative on Methods, Measurement, and
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5 Pain Assessment in Clinical Trials.^{17,18} Discrepancies were resolved by discussion or, when
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7 necessary, by an adjudicator.
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11 **Risk of Bias Assessment**
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14 Risk of bias was assessed for eligible studies, independently and in duplicate, by pairs of
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16 reviewers using a modified Cochrane risk of bias instrument (RoB 1.0) according to the
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18 following domains: random sequence generation, allocation concealment, blinding of
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20 participants, caregivers, outcome assessors, and data analysts, and loss to follow-up ($\geq 20\%$).
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22 missing data was considered high risk of bias).^{19,20}
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26 **Data Analysis**
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30 We converted continuous measures to common scales on a domain-by-domain basis when
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32 different instruments were used to measure the same construct: (1) pain relief to a 10cm visual
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34 analogue scale (VAS); (2) physical functioning to the 100-point 36-item Short Form Survey (SF-
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36 36) physical component summary (PCS) score; (3) emotional functioning to the 100-point SF-36
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38 mental component summary (MCS) score; (4) role functioning to the 100-point SF-36 subscale
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40 for role limitations due to physical problems; (5) social functioning to the 100-point SF-36
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42 subscale for social functioning; and (6) sleep quality to a 100-mm VAS.²¹
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49 We calculated direct estimates for any comparison reported by two or more studies as the
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51 weighted mean difference (WMD) and associated 95% credible interval (95% CrI) using change
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53 score from baseline to the end of follow-up to address interpatient variability. When standard
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3 deviations (SDs) for continuous outcomes were not reported by study authors, they were
4 estimated using confidence intervals or exact p-values.²² To optimize interpretability of our
5 findings for statistically significant continuous outcomes, we used the network estimate of
6 treatment effects to model the risk difference (RD) for achieving the minimally important
7 difference (MID) or higher. We used an MID of 1cm for the 10-cm VAS for pain,²³ 10mm for
8 sleep quality, 10-points for SF-36 subscales (role and social functioning), and 5-points for SF-36
9 PCS and MCS scores.^{24,25}

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21 For discontinuations due to adverse events, we used a binomial likelihood distribution and logit
22 link to generate the pooled odds ratio (OR) with corresponding 95% CrI. We constructed
23 separate models for enriched and non-enriched trials, as enriched trials typically exclude patients
24 who report problematic adverse events during an open-label run-in period prior to
25 randomization.²⁶ For estimating the number of patients expected to discontinue due to adverse
26 events, we calculated the absolute effects for network estimates by multiplying the OR and its
27 95% CrI with the estimated baseline risk for discontinuations due to adverse events. We used
28 median risk in the placebo group of included randomized trials as the baseline risk.

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38 For studies that reported outcomes at several timepoints, we used data from the longest follow-
39 up. We performed all conventional pairwise meta-analyses using DerSimonian and Laird
40 random-effects models. Heterogeneity between RCTs for each direct comparison was assessed
41 with visual inspection of forest plots and the I² statistic.²⁷ For all direct comparisons, we assessed
42 small study effects using funnel plots and Egger's test when 10 or more trials were available.²⁸

We used edge-splitting (side-splitting) to evaluate the consistency of relative treatment effects between direct (e.g. pairwise meta-analysis) and indirect evidence, and leverage plots to visually inspect model fit.²⁹ Models were programmed with three chains, and the convergence assessed using the Gelman-Rubin statistic.³⁰ All analyses began with a burn-in phase (1000 iterations) followed by 100 000 iterations with 1000 adaptations. We used non-informative priors with mean 0 and standard deviation 15u, where u is the largest maximum likelihood estimator of treatment differences on the linear scale in single trials.³¹ Statistical superiority was asserted when the 95% CrI excluded the null effect (i.e., 0.0 for WMDs and 1.0 for ORs). All analyses were programmed in R v3.5.3 (<https://www.R-project.org>) using BUGSnet.³¹

We tested the following a priori subgroup hypotheses that treatment effects were associated with: (1) neuropathic vs. non-neuropathic pain; (2) shorter vs. longer (≤ 2 months vs > 2 months) follow-up; (3) trials at risk of bias (on a criterion-by-criterion basis); (4) enriched enrollment trials vs not enriched; and (5) higher opioid doses versus lower opioid doses by evaluating the following morphine milligram equivalent (MME) per day thresholds: (i) high = MME > 100 mg; (ii) intermediate = MME 50 – 99 mg; and (iii) low = MME < 50 mg. We assessed the credibility of significant subgroup effects (i.e., test of interaction $p \leq 0.05$) with the ICEMAN tool.³² We used network meta-regression to explore the association between treatment effects and length of follow-up and sample size. The deviance information criterion (DIC) was used to assess model fit.

Quality of Evidence

We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach to assess certainty of the evidence for all outcomes and effect estimates from network meta-analysis.³³ Ratings of the certainty of evidence for direct and indirect estimates included assessment of risk of bias, inconsistency, indirectness, publication bias, and intransitivity (only for indirect estimates). We judged network estimates as imprecise if the 95% CrI included half the MID for continuous outcomes (e.g., 0.5 cm for pain) or the null effect (OR of 1) for discontinuation due to adverse events.

Role of the funding source

The funders had no role in study design, data collection, analysis, interpretation or writing of the manuscript, or the decision to submit.

Patient and Public Involvement

Patients and public were not involved in this research.

Results

Of 20 012 citations identified, 90 studies from 89 publications proved eligible for review (Figure 1, eAppendix 2-3 in Supplement). No trials of inhaled cannabis were eligible for our review due to inadequate duration of follow-up (<4 weeks). Sixty-six trials compared opioids to placebo, 23 trials compared medical cannabis to placebo, and 1 trial³⁴ randomized patients to nabilone or dihydrocodeine. Among the included studies, the median of the mean age of participants was 56 years (interquartile range [IQR] 50 to 62), 58% were female, the median of the mean duration of pain was 8.1 years (IQR 5.0 to 12.7), and the median of the mean pain score at enrollment was 6.05 (IQR 4.65 to 6.90). Twenty-nine trials enrolled patients with neuropathic pain, 60 with non-neuropathic pain, and 1 trial enrolled patients with mixed pain. (Table 1, eTable 1 in Supplement)

Table 1: Summary of study participant characteristics included in eligible randomized control trials

No of trials	No of patients	Age, median of mean (IQR)	% female, median of mean (IQR)	Baseline pain score, median of mean (min – max)	No of studies by pain type*	No of studies by Intervention dose/format*	Follow-up, median days (min – max)	Trial type*	Source of funding*	No of studies with adequate randomization*	No of studies with adequate concealment*	No of studies with adequate blinding*
Opioids versus placebo												
66	18,401	58 (50 to 62)	56 (44.5 to 62)	6.01 (1.87-7.83)	Neuropathic pain, n = 18 (27%) Non-neuropathic, n = 47 (71%) Mixed, n = 1 (2%)	MME > 90mg, n = 14 (21%) MME 50 – 90mg, n = 19 (29%) MME < 50 mg, n = 21 (32%) Dose details Not reported n = 12 (18%)	84 (28–180)	Enriched n = 20 (30%) Non-enriched n = 46 (70%)	No industry funding, n = 7 (11%) Industry funding, n = 54 (82%) Not reported, n = 5 (8%)	37 (56%)	40 (61%)	65 (98%)
Medical cannabis versus placebo												
23	3,435	53 (50 to 58)	62 (40 to 70)	6.28 (2.15–7.80)	Neuropathic pain, n = 10 (43%) Non-neuropathic, n = 13 (57%)	PEA, n = 2 (9%) THC/CBD, n = 11 (48%) THC, n = 7 (30%) CBD n = 2 (9%) CBDC n = 1 (4%)	51 (28–112)	Enriched n = 3 (13%) Non-enriched n = 20 (87%)	No industry funding, n = 6 (26%) Industry funding, n = 15 (65%) Not reported, N = 2 (9%)	15 (65%)	23 (100%)	23 (100%)
Medical cannabis versus opioids												
1	192	50	26	6.72	Neuropathic pain, n = 1 (100%)	THC, n = 1 (100%)	42	Non-enriched n = (100%)	Industry funding, n = 1 (100%)	1 (100%)	1 (100%)	1 (100%)

* Values in parenthesis are percentage of trials

**IQR, interquartile range.

CBDV, Cannibidiolvarin

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5 Most trials (75 of 90; 83%) were judged to be at high risk of bias for at least one domain.
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7 Adequate generation of a randomization sequence was reported by 53 (59%) trials, 64 (71%)
8 reported concealment of allocation, and almost all trials reported blinding of patients (99%) and
9 healthcare providers and data collectors (98%). Sixty-five (72%) trials reported $\geq 20\%$ missing
10 outcome data. (eTable 2 in Supplement). We did not find evidence of incoherence. For closed
11 loop networks, consistency was met based on DIC values. For open loop networks, direct and
12 indirect estimates are reported separately. (eTable 1-4 & eFigure 1 in Supplement).
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24 Moderate certainty evidence showed that, compared to placebo, opioids provide small
25 improvements in pain (modelled RD for achieving the MID 15%, 95% CrI 13 to 17), physical
26 functioning (modelled RD for achieving the MID 5%, 95% CrI 3 to 8), and sleep quality
27 (modelled RD for achieving the MID 8%, 95% CrI 4 to 13). Low to moderate certainty evidence
28 supported similar effects for medical cannabis vs. placebo. Neither were more effective than
29 placebo for role, social, or emotional functioning (all high to moderate certainty evidence).
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31 (Table 2, eTable 2 &, eFigure 2-13 in Supplement).
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42 Low certainty evidence from 82 RCTs involving 19 693 patients suggested that there may be
43 little to no difference in pain relief between medical cannabis and opioids (WMD 0.23cm on a
44 10cm VAS, 95% CrI -0.06 to 0.53). (Table 2, eFigure 1 & eTable 4 in Supplement). Moderate
45 certainty evidence from 44 RCTs involving 12 727 patients shows there is probably little to no
46 difference in physical functioning with medical cannabis compared to opioids (WMD 0.47 points
47 on the 100-point SF-36 PSC score, 95% CrI -1.97 to 2.99). (Table 2, eTable 3 in Supplement).
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3 Low certainty evidence from 32 RCTs involving 8 201 patients suggests that there may be little
4 to no difference in sleep quality between medical cannabis and opioids (WMD 0.49mm on a
5 100mm VAS, 95% CrI -4.72 to 5.59). (Table 2, eTable 3 in Supplement). There were insufficient
6 data to construct networks for health-related quality of life (eAppendix 4 in Supplement).
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15 Discontinuations due to adverse events were reported in 22 enrichment trials (6 831 patients) and
16 in 51 non-enrichment trials (13 012 patients). Among enrichment trials, low certainty evidence
17 suggests that there may be little to no difference in discontinuations due to adverse events
18 between medical cannabis and opioids (OR 0.77, 95% CrI 0.07 to 8.83). Moderate certainty
19 evidence shows that in non-enriched studies, discontinuations due to adverse events are probably
20 less for medical cannabis vs. opioids (OR 0.55, 95% CrI 0.36 to 0.83). (Table 2). Moderate and
21 high certainty evidence showed that, compared to placebo, opioids and medical cannabis,
22 respectively, probably results in higher discontinuations compared to placebo (modelled RD for
23 achieving the MID for opioids vs. placebo, 10%, 95% CrI 8% to 12%; medical cannabis vs.
24 placebo, 4%, 95% CrI 1% to 7%). (Table 2, eFigure 14-17 in Supplement).
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We found no evidence of credible subgroup effects based on type of pain condition, length of follow-up, sample size, or opioid dose (Table 3, eTable 5-10 in Supplement).

Table 2: Treatment effects and certainty of evidence (GRADE) for opioids and medical cannabis in patients with chronic noncancer pain

Comparison	Direct evidence		Indirect evidence		Network estimate WMD (95% CrI)	RD for achieving the MID (95% CI)	GRADE
	no. of trials (patients)	Treatment effect WMD* (95% CI)	no. of trials (patients)	Treatment effect WMD* (95% CI)			
Pain relief: 10cm VAS for pain; lower is better; MID = 1cm							
Opioids vs. placebo	62 (17,431)	-0.84 (-0.99 to -0.69)	62 (17,431)	-0.83 (-0.97 to -0.70)	-0.83 (-0.97 to -0.70)	15% (13% to 17%)	Moderate
Medical cannabis vs. placebo	19 (2,116)	-0.63 (-0.94 to -0.32)	19 (2,116)	-0.59 (-0.88 to -0.32)	-0.60 (-0.87 to -0.33)	11% (6% to 15%)	Low
Medical cannabis vs. opioids	1 (146)	0.13 (-0.54 to 0.80)	81 (19,547)	0.24 (-0.07 to 0.55)	0.23 (-0.06, 0.53)	-	Low
Physical functioning: 0-100 point SF-36 PCS score; higher is better; MID = 5-points							
Opioids vs. placebo	32 (10,926)	2.38 (1.05 to 3.72)	-	-	2.05 (1.01, 3.29)	5% (3% to 8%)	Moderate
Medical cannabis vs. placebo	12 (1,801)	3.00 (0.08 to 5.91)	-	-	2.52 (0.37, 4.91)	6% (1% to 12%)	Moderate
Medical cannabis vs. opioids	-	-	44 (12,727)	0.47 (-1.97 to 2.99)	0.47 (-1.97 to 2.99)	-	Moderate
Emotional functioning: 0-100 point SF-36 MCS score; higher is better; MID = 5-points							
Opioids vs. placebo	22 (7,267)	-0.00 (-1.09 to 1.09)	-	-	-0.15 (-1.10 to 0.92)	-	High
Medical cannabis vs. placebo	8 (1,515)	0.72 (-1.01 to 2.45)	-	-	0.70 (-1.42 to 2.84)	-	Moderate
Medical cannabis vs. opioids	-	-	30 (8,782)	0.85 (-1.55 to 3.18)	0.85 (-1.55 to 3.18)	-	Low
Role functioning: 0-100 point SF-36 subscale for role limitations due to physical problems; higher is better; MID = 10-points							
Opioids vs. placebo	13 (3,661)	0.91 (-1.17 to 2.98)	-	-	0.94 (-1.26 to 3.17)	-	Moderate
Medical cannabis vs. placebo	5 (528)	1.27 (-12.39 to 14.93)	-	-	0.88 (-3.78 to 6.05)	-	Moderate
Medical cannabis vs. opioids	-	-	18 (4,189)	-0.05 (-5.16 to 5.60)	-0.05 (-5.16 to 5.60)	-	Moderate
Social functioning: 0-100 point SF-36 subscale for social functioning; higher is better; MID = 10-points							
Opioids vs. placebo	14 (4,075)	0.47 (-1.47 to 2.41)	-	-	1.17 (-1.72 to 4.58)	-	Moderate
Medical cannabis vs. placebo	6 (795)	-1.82 (-5.79 to 2.15)	-	-	1.70 (-3.28 to 8.13)	-	Moderate
Medical cannabis vs. opioids	-	-	20 (4,870)	0.55 (-5.34 to 7.41)	0.55 (-5.34 to 7.41)	-	Moderate
Sleep quality: 100mm VAS for sleep quality; higher is better; MID = 100mm							
Opioids vs. placebo	21 (6,677)	5.55 (2.67 to 8.43)	-	-	5.46 (2.62 to 8.59)	8% (4% to 13%)	Moderate
Medical cannabis vs. placebo	11 (1,524)	6.04 (1.43 to 10.66)	-	-	5.95 (1.82 to 10.24)	9% (3% to 15%)	Low
Medical cannabis vs. opioids	-	-	32 (8,201)	0.49 (-4.72 to 5.59)	0.49 (-4.72 to 5.59)	-	Low
Discontinuations due to adverse events (enriched trials)							
Opioids vs. placebo	20 (6,699)	OR, 1.39 (1.04 to 1.86)	-	-	OR, 1.25 (0.91, 1.67)	-	Low
Medical cannabis vs. placebo	2 (132)	OR, 5.00 (0.25 to 101.7)	-	-	OR, 0.96 (0.09 to 10.80)	-	Low
Medical cannabis vs. opioids	-	-	22 (6,831)	OR, 0.77 (0.07, 8.83)	OR, 0.77 (0.07 to 8.83)	-	Low
Discontinuations due to adverse events (non-enriched trials)							
Opioids vs. placebo	35 (11,019)	OR, 3.58 (3.00 to 4.27)	35 (11,019)	OR, 3.27 (2.70 to 3.93)	OR, 3.27 (2.71 to 3.90)	10% (8% to 12%)	Moderate
Medical cannabis vs. placebo	15 (1,801)	OR, 2.47 (1.49 to 4.11)	15 (1,801)	OR, 1.78 (1.15 to 2.63)	OR, 1.80 (1.19 to 2.63)	4% (1% to 7%)	High
Medical cannabis vs. opioids	1 (192)	OR, 0.50 (0.16, 1.61)	50 (12,820)	OR, 0.54 (0.34 to 0.84)	OR, 0.55 (0.36 to 0.83)	-	Moderate

OR = odds ratio. RD = risk difference and represents the percentage of patients achieved at or above MID. WMD = weighted mean difference

Table 3: Subgroup analysis for pain and secondary outcomes with moderate to high certainty evidence

Subgroup factors		Pain relief			Physical functioning			Role functioning			Social functioning			Discontinuations due to adverse events (non-enriched)			
		No studies	WMD 95% CrI	p-value	No studies	WMD 95% CrI	p-value	No studies	WMD 95% CrI	p-value	No studies	WMD 95% CrI	p-value	No studies	OR 95% CrI	p-value	
Clinical condition	Neuropathic	26	0.74 (0.30,1.12)	0.004	11	-0.67 (-4.46, 3.28)	0.55	8	-4.66 (-21.16,5.49)	0.10	8	-8.09 (-16.89,-0.69)	0.047	17	0.91 (0.48, 1.76)	0.052	
	Non-neuropathic	55	-0.12 (-0.55,0.30)		32	0.97 (-2.67, 4.72)		9	9.81 (-1.55,21.10)		11	1.01 (-3.01,4.75)		33	*0.34* (0.15, 0.67)		
Length of follow-u	≤ 2 months	39	0.04 (-0.36,0.45)	0.228	17	2.35 (-2.72,6.56)	0.59	10	8.59 (-3.64,20.37)	0.14	10	-0.31 (-8.27,7.79)	0.70	29	*0.42* (0.20, 0.79)	0.338	
	>2 months	43	0.41 (-0.04,0.85)		27	-0.75 (-3.83, 2.38)		8	-2.48 (-11.89, 5.23)		10	-2.26 (-9.50,2.29)		22	0.65 (0.37, 1.16)		
Adequate randomization	Yes	49	0.14 (-0.25,0.53)	0.506	31	0.36 (-2.14, 3.03)	0.95	11	2.92 (-9.96,15.78)	0.55	15	0.07 (-4.45,4.34)	0.35	36	*0.48* (0.27, 0.79)	0.375	
	No	33	0.37 (-0.19,0.92)		13	0.01 (-10.42, 9.03)		7	-4.55 (-26.29,14.71)		5	-6.93 (-21.75,6.27)		15	0.77 (0.31, 1.86)		
Adequate concealment	Yes	59	0.25 (-0.08,0.58)	NA	34	0.87 (-1.43, 3.37)	NA	13	-0.81 (-6.88,5.75)	NA	16	-2.02 (-6.75,1.60)	NA	39	*0.51* (0.31, 0.79)	NA	
	No	NA	NA		NA	NA		NA	NA		NA	NA		NA	NA		
Industry funded trials	Yes	65	0.23 (-0.13,0.58)	0.877	35	0.72 (-2.02, 3.52)	0.36	13	-0.71 (-6.86,5.72)	0.66	16	-0.62 (-4.94,2.69)	1.00	39	*0.55* (0.33, 0.92)	0.484	
	No	10	0.32 (-0.78,1.39)		6	-4.57 (-15.20, 6.66)		5	-4.59 (-18.01,14.04)		4	-0.62 (-10.78,10.11)		6	0.77 (0.09, 3.75)		
Loss to follow-up	High (≥20%)	60	*0.53* (0.08,0.98)	0.074	34	-0.39 (-5.45, 4.52)		14	1.40 (-3.77, 8.21)	0.21	15	-3.31 (-8.10,1.48)	0.66	37	0.63 (0.36, 1.11)	0.790	
	Low (<20%)	22	-0.09 (-0.64,0.38)		10	0.86 (-3.74, 6.97)		4	-18.49 (-51.56,8.85)		5	0.32 (-17.97,13.13)		14	0.79 (0.13, 2.97)		
Study design	Enrichment	22	-0.65 (-1.65,0.35)	0.093	NA	NA	NA	3	-22.92 (-61.99,16.11)	0.24	3	-14.19 (-40.56,12.39)	0.36	NA			
	Non-enrichment	60	0.25 (-0.07,0.57)		34	0.37 (-2.57, 3.19)		15	0.55 (-5.34, 7.41)		17	-1.54 (-6.21,2.32)					

All values in bold are statistically significant at the 0.05 significance level. * = unless otherwise indicated. Results are medical cannabis versus opioids. p-value based on test of interaction

Discussion

This network meta-analysis of 90 trials that enrolled 22 028 people living with chronic noncancer pain provides low certainty evidence that medical cannabis is similarly effective to opioids for pain relief and sleep quality, and moderate certainty evidence for similar effects on physical functioning. The magnitude of effects vs. placebo for medical cannabis or opioids was modest, with the modelled RD for achieving the MID for pain, function and sleep ranging from 5% to 15%. Moderate certainty evidence also suggests that use of medical cannabis vs. opioids resulted in fewer discontinuations due to adverse events. Moderate to high certainty evidence showed that neither opioids nor medical cannabis were effective for improving emotional, social or role functioning among people living with chronic pain.

Our study, which is the first network meta-analysis exploring the comparative effectiveness of medical cannabis and opioids for chronic noncancer pain, has several strengths. We used the GRADE approach to appraise the certainty of evidence for treatment effects and followed GRADE guidance for communicate our findings. We evaluated harms using discontinuations due to adverse events to facilitate pooling across trials. Further, we explored subgroup effects and assessed their credibility according to current best practices.

Clinical guidelines for chronic noncancer pain recommend optimization of nonopioid based pharmacologic and non-pharmacologic therapies prior to initiating opioids.³⁵⁻³⁷ However, approximately a third of all patients living with chronic noncancer pain are prescribed opioids³⁸; and increasing concerns regarding harms of long-term opioid therapy has generated enthusiasm

for alternatives, including medical cannabis.³⁹ In part, because some observational studies (but not others^{40,41}) have shown an association between legalization of cannabis and reduced prevalence of opioid use disorder and opioid overdose.^{42,43} Moreover, users of medical cannabis acknowledge substitution of prescription medication, particularly opioids, as a common motive.^{44,45} This issue is controversial⁴⁶, however, and recent guidelines have provided conflicting recommendations regarding the effectiveness of medical cannabis for chronic pain and whether use of cannabis reduces opioid consumption.^{11-13,47} An important limitation of prior evidence syntheses is the scarcity of trials directly comparing medical cannabis against opioids for chronic pain. These treatment options are mostly trialed against placebo, and network meta-analysis can therefore establish comparative effectiveness by virtue of this common compactor. Our findings suggest that both opioids and medical cannabis may provide benefits for a minority of chronic pain patients (e.g., compared to placebo, 10-15% of patients experience a 1cm or greater relief in pain on a 10cm scale). However, reviews of patient values and preferences show that people living with chronic pain place high value on the possibility of achieving small but important pain relief.^{48,49} Furthermore, cannabis does not cause respiratory depression which can result from opioids consumption and lead to non-fatal or fatal overdose.⁵⁰

Future research should directly compare the effectiveness of opioids vs. medical cannabis for chronic pain, and follow patients sufficiently to inform long-term benefits and harms. Trials should report all outcomes measures of importance to people who live with chronic pain.^{17,18,51} Randomized trials are also needed to establish opioid-substitution effects of medical cannabis for chronic pain, and observational studies to inform long-term and infrequent harms of both medical cannabis and opioids for chronic pain (e.g., overdose, addiction).

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3 There are some limitations associated with our study. None of the trials eligible for our review
4 explored inhaled cannabis, and our results may not be generalizable to this method of
5 administration. We pooled different opioids and types of cannabis; however, subgroup analysis
6 suggests that effects for chronic pain are similar across different opioids and medical cannabis
7 products.^{52,53} Further, a network meta-analysis found no evidence to support important
8 differences in pain relief, functional improvement, or gastrointestinal adverse events between
9 different types of opioids.⁵² Both opioids and cannabis can result in use disorders and overdose;
10 however, we were unable to construct a network to explore the comparative risk of these
11 important harms due to lack of reporting among clinical trials.

Conclusions

In this network meta-analysis of randomized trials of patients with chronic noncancer pain, low to moderate certainty evidence suggests that medical cannabis may provide similarly small improvements in pain, physical function, and sleep compared to opioids, and fewer discontinuations due to adverse events.

For peer review only

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3 **Contributors:** HMJ, JWB, BS, ML and JET conceived and designed the study. HMJ, LW, AN
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5 performed the statistical analyses. All authors interpreted the data and could access data included
6 in the study. HMJ, JWB and JET drafted the manuscript. All authors made critical revisions to
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24 **Ethical approval:** Not required.
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29
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49 **Transparency:** The lead authors affirm that the manuscript is an honest, accurate, and
50 transparent account of the study being reported; that no important aspects of the study have been
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3 omitted; and that any discrepancies from the study as originally planned (and, if relevant,
4
5 registered) have been explained.
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5 **Figure 1: Study Selection Process for the Systematic Review and Meta-Analysis**

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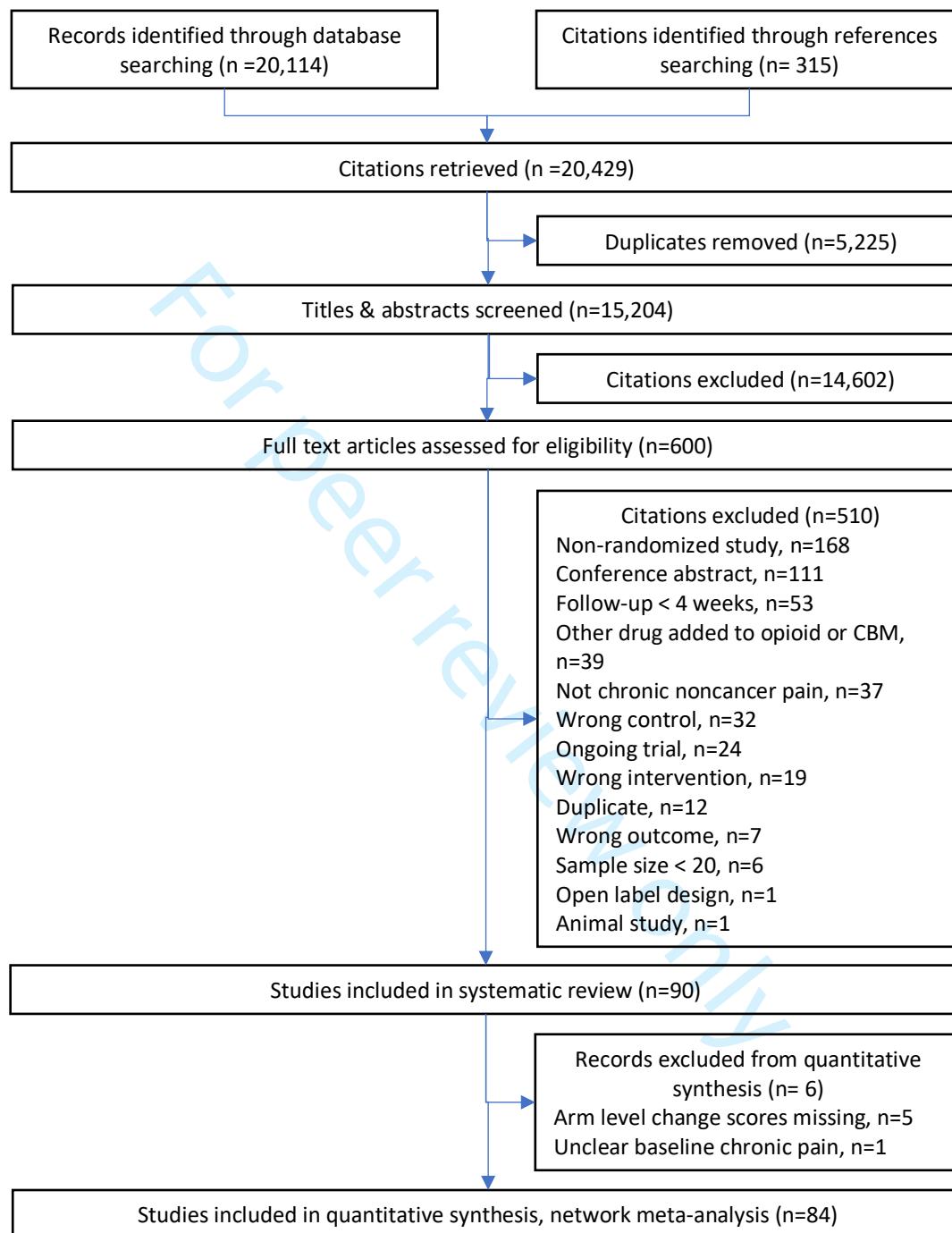
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36 observational studies. *BMJ Open*. 2021;11(7):e047717. doi:[10.1136/bmjopen-2020-047717](https://doi.org/10.1136/bmjopen-2020-047717)
- 37 48 Goshua A, Craigie S, Guyatt GH, et al. Patient Values and Preferences Regarding Opioids for
38 Chronic Noncancer Pain: A Systematic Review. *Pain Med*. 2018;19(12):2469-2480.
39 doi:[10.1093/pmt/pnx274](https://doi.org/10.1093/pmt/pnx274)
- 40 49 Zeng L, Lytvyn L, Wang X, et al. Values and preferences towards medical cannabis among people
41 living with chronic pain: a mixed-methods systematic review. *BMJ Open*. 2021;11(9):e050831.
42 doi:[10.1136/bmjopen-2021-050831](https://doi.org/10.1136/bmjopen-2021-050831)
- 43 50 Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Prescription of Long-Acting Opioids and
44 Mortality in Patients With Chronic Noncancer Pain. *JAMA*. 2016;315(22):2415.
45 doi:[10.1001/jama.2016.7789](https://doi.org/10.1001/jama.2016.7789)
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3 51 Mulla SM, Maqbool A, Sivananthan L, et al. Reporting of IMMPACT-recommended core outcome
4 domains among trials assessing opioids for chronic non-cancer pain. *Pain*. 2015;156(9):1615-1619.
5 doi:[10.1097/j.pain.0000000000000241](https://doi.org/10.1097/j.pain.0000000000000241)
- 6 52 Noori A, Sadeghirad B, Wang L, et al. Comparative benefits and harms of individual opioids for
7 chronic non-cancer pain: a systematic review and network meta-analysis of randomised trials. *Br J
8 Anaesth*. Published online July 8, 2022:S0007-0912(22)00288-4. doi:[10.1016/j.bja.2022.05.031](https://doi.org/10.1016/j.bja.2022.05.031)
- 9 53 Wang L, Hong PJ, May C, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer
10 related pain: a systematic review and meta-analysis of randomised clinical trials. *BMJ*.
11 2021;374:n1034. doi:[10.1136/bmj.n1034](https://doi.org/10.1136/bmj.n1034)
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eAppendix 1: Literature search strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Search Strategy:

1 (chronic adj4 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (58120)
2 Chronic Pain/ (9487)
3 exp Osteoarthritis/ (54546)
4 osteoarthritis*.mp. (75997)
5 osteo-arthritis.mp. (367)
6 degenerative arthrit*.mp. (1219)
7 exp Arthritis, Rheumatoid/ (104666)
8 exp Neuralgia/ (17706)
9 Diabetic Neuropathies/ (13601)
10 (neuropath* adj5 (pain* or diabet*)).mp. (36937)
11 neuralg*.mp. (23772)
12 zoster.mp. (19225)
13 Irritable Bowel Syndrome/ (6066)
14 (IBS or irritable colon or irritable bowel).mp. (14347)
15 Migraine Disorders/ (23014)
16 migraine.mp. (34507)
17 Fibromyalgia/ (7573)
18 fibromyalg*.mp. (10324)
19 complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ (5219)
20 (complex regional pain syndromes or causalgia).mp. (2139)
21 Pain, Intractable/ (6021)
22 Phantom Limb/ (1737)
23 Hyperalgesia/ (10026)
24 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*).adj3 pain).mp. (16519)
25 or/1-24 (374187)
26 exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ (34838)
27 Radiculopathy/ or radiculopathy.mp. (8057)
28 musculoskeletal pain/ or headache/ (27891)
29 exp Arthralgia/ (10991)
30 exp Headache Disorders/ (31166)
31 headache*.mp. (83353)
32 Temporomandibular Joint Dysfunction Syndrome/ (4838)
33 ((TMJ or TMJD) and pain*).mp. (2434)
34 whiplash.mp. or exp whiplash injury/ (3756)
35 exp Cumulative Trauma Disorders/ (12612)
36 exp Peripheral Nervous System Diseases/dt [Drug Therapy] (12959)
37 Pain Measurement/de [Drug Effects] (6352)
38 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodynji* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (39779)
39 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (144063)
40 or/26-39 (299548)
41 (acute or emergency or preoperative or postoperative).ti,ab. (1700816)
42 40 not 41 (252546)
43 25 or 42 (532409)
44 exp Analgesics, Opioid/ (103616)

1
2
3 45 (opioid* or opiate*).mp. (114059)
4 46 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or
5 dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or
6 ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or
7 levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine
8 or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or
9 promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.(143753)
10 47 or/44-46 (199233)
11 48 exp Narcotics/ (111500)
12 49 narcotic*.mp. (57165)
13 50 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgin or biokanol or Codinovo
14 or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or
15 dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or
16 duromorph or duragesic or durogesic or eucodal or Fedotzine or Fenantest or Fentora or Fortral or Hycodan or
17 Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or
18 isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or
19 lexir or lidol or lydol or morfin or morphia or morphin or morphinium or morphinene or morphium or ms
20 contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or
21 oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or
22 skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or
23 tramadolhameln or tramadol or tramadura or tramagetic or tramagit or tramal or tramex or tramundin
24 or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin
25 or tramadoc or ultram or zamudol or zumalgie or zydol or zytram).mp. [mp=title, abstract, original title, name of
26 substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease
supplementary concept word, unique identifier, synonyms] (9563)
27 51 or/44-50 (227775)
28 52 43 and 51 (22678)
29 53 epidemiologic studies/ (7641)
30 54 exp Case-Control Studies/ (904344)
31 55 exp Cohort Studies/ (1723417)
32 56 Case control.tw. (106622)
33 57 (cohort adj (study or studies)).tw. (151570)
34 58 Cohort analy\$.tw. (6083)
35 59 (Follow up adj (study or studies)).tw. (44718)
36 60 ((observational or epidemiol*) adj (study or studies)).tw. (156420)
37 61 Longitudinal.tw. (201362)
38 62 Retrospective.mp. or prospective.tw. (1247587)
39 63 Cross sectional.tw. (272577)
40 64 Cross-sectional studies/ (260504)
41 65 or/53-64 (2717825)
42 66 exp animals/ not humans.sh. (4438182)
43 67 65 not 66 (2649950)
44 68 52 and 67 (3763)
45 69 randomized controlled trial.pt. (456617)
46 70 controlled clinical trial.pt. (92277)
47 71 randomized.ab. (406479)
48 72 placebo.ab. (187496)
49 73 drug therapy.fs. (2003496)
50 74 randomly.ab. (287373)
51 75 trial.ab. (422125)
52 76 groups.ab. (1777409)
53 77 or/69-76 (4167722)
54 78 clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs. (5199787)
55 79 randomized controlled trial.pt. or randomized controlled trial.mp. (476635)
56 80 randomized controlled trial.pt. or randomized.mp. or placebo.mp. (790362)
57 81 or/78-80 (5214838)
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1
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3 82 77 or 81 (6680171)
4 83 exp animals/ not humans.sh. (4438182)
5 84 82 not 83 (5604099)
6 85 43 and 51 and 84 (14496)
7 86 limit 85 to yr="2010 -Current" (6438)
8 87 68 or 86 (8377)
9 88 (MEDLINE or systematic review or literature search).tw. or meta analysis.mp,pt. (256038)
10 89 43 and 51 and 88 (881)
11 90 87 or 89 (8697)
12 91 exp Sleep Apnea Syndromes/ (30607)
13 92 sleep apn?ea.mp. (38637)
14 93 sleep-disordered breathing.mp. (5685)
15 94 hypogonadism.mp. or Hypogonadism/ (13040)
16 95 ((testosterone or androgen) and (deprivation or deficiency)).mp. (12336)
17 96 OPIAD.mp. (10)
18 97 or/91-96 (64161)
19 98 52 and 97 (144)
20 99 90 or 98 (8736)

21 **PsycInfo**

22 **Database: PsycINFO via OVID**

23 Search Strategy:

24 1 (chronic adj4 pain*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests &
25 measures] (19944)
26 2 chronic pain/ (12078)
27 3 exp arthritis/ (3853)
28 4 osteoarthritis*.mp. (1758)
29 5 osteo-arthritis.mp. (8)
30 6 degenerative arthrit*.mp. (15)
31 7 exp neuralgia/ (892)
32 8 exp neuropathy/ (5931)
33 9 (neuropath* adj5 (pain* or diabet*)).mp. (6256)
34 10 neuralg*.mp. (1530)
35 11 zoster.mp. (550)
36 12 irritable bowel syndrome/ (1055)
37 13 (IBS or irritable colon or irritable bowel).mp. [mp=title, abstract, heading word, table of contents, key
38 concepts, original title, tests & measures] (1832)
39 14 migraine headache/ (8772)
40 15 migraine.mp. (11715)
41 16 fibromyalgia/ (1768)
42 17 fibromyalg*.mp. (3042)
43 18 complex regional pain syndromes.mp. (55)
44 19 "complex regional pain syndrome (type i)"/ (137)
45 20 (complex regional pain syndromes or causalgia).mp. (109)
46 21 somatosensory disorders/ (1266)
47 22 hyperalgesi*.mp. (3914)
48 23 somatoform pain disorder/ (801)
49 24 somatoform disorders/ (7528)
50 25 conversion disorder/ (998)
51 26 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (3008)
52 27 or/1-26 (58879)
53 28 back pain.mp. or exp Back Pain/ (5353)
54 29 radiculopathy.mp. (202)
55 30 musculoskeletal pain.mp. (1410)
56 31 Arthralgia.mp. (105)
57 32 headache.mp. or exp HEADACHE/ (19164)

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3 33 ((TMJ or TMJD) and pain*).mp. (142)
4 34 WHIPLASH/ or whiplash.mp. (571)
5 35 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi*
6 or myodyn* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (5452)
7 36 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint*
8 or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or
9 cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (18302)
10 37 or/28-36 (39808)
11 38 (acute or emergency or preoperative or postoperative).ti,ab. (111436)
12 39 37 not 38 (35095)
13 40 27 or 39 (71492)
14 41 exp opiates/ (22978)
15 42 (opioid* or opiate*).mp. (27750)
16 43 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or
17 dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or
18 ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or
19 levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine
20 or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or
21 promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (27830)
22 44 exp narcotic drugs/ (27031)
23 45 narcotic*.mp. (5729)
24 46 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodaligic or biokanol or Codinovo
25 or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or
26 dihydronine or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or
27 duromorph or duragesic or durogesic or eucodal or Fedotzine or Fenantest or Fentora or Fortral or Hycodan or
28 Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or
29 isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or
30 lexit or lidol or lydol or morfin or morphia or morphin or morphinium or morphinene or morphium or ms
31 contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or
32 oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or
33 skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or
34 tramadolhameln or tramadol or tramadura or tramagetic or tramagit or tramek or tramal or tramex or tramundin
35 or trasedal or theradol or tiral or topalgeic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin
36 or tramadoc or ultram or zamudol or zumalgec or zydol or zytram).mp. (928)
37 47 or/41-46 (47945)
38 48 37 and 47 (2028)
39 49 animals/ not humans/ (7067)
40 50 animal models/ (29760)
41 51 animal research/ (368)
42 52 exp rodents/ (201732)
43 53 (rat or rats or mouse or mice).ti. (110418)
44 54 or/49-53 (226624)
45 55 48 not 54 (1547)

46 **Database: AMED (Allied and Complementary Medicine) via OVID**

47 Search Strategy:

48 1 analgesics opioid/ (335)
49 2 (opioid* or opiate*).mp. (1449)
50 3 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or
51 dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or
52 ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or
53 levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine
54 or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or
55 promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. [mp=abstract, heading words,
title] (1097)
56 4 narcotics/ (177)

1
2
3 5 narcotic*.mp. (345)
4 6 (adolonta or Anpec or Ardinex or Asimadoline or Alvimap or amadol or biodalgi or biokanol or Codinovo
5 or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or
6 dihydronine or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or
7 duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or
8 Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or
9 isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or
10 lexit or lidol or lydol or morfin or morphia or morphin or morphinium or morphinene or morphium or ms
11 contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or
12 oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or
13 skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or
14 tramadolhameln or tramadol or tramadolor or tramadura or tramagetic or tramagit or trameke or tramal or tramex or tramundin
15 or trasedal or theradol or tiral or topalgi or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin
16 or tramadoc or ultram or zamudol or zumalgi or zydot or zytram).mp. [mp=abstract, heading words, title] (109)
7 or/1-6 (2268)
8 (chronic adj4 pain).mp. [mp=abstract, heading words, title] (4640)
9 exp arthritis/ (5636)
10 arthralgia/ (189)
11 fibromyalgia/ (1656)
12 neuralgia/ (157)
13 diabetic neuropathies/ (264)
14 (neuropath* adj5 (pain* or diabet*)).mp. (981)
15 neuralg*.mp. [mp=abstract, heading words, title] (335)
16 osteoarthrit*.mp. [mp=abstract, heading words, title] (3321)
17 irritable bowel syndrome/ (133)
18 (IBS or irritable colon or irritable bowel).mp. [mp=abstract, heading words, title] (297)
19 fibromyalg*.mp. [mp=abstract, heading words, title] (1846)
20 Migraine/ or migraine.mp. (651)
21 complex regional pain syndromes/ or reflex sympathetic dystrophy/ (188)
22 (complex regional pain syndromes or causalgia).mp. [mp=abstract, heading words, title] (77)
23 pain intractable/ (431)
24 hyperalgesia/ or phantom limb/ (181)
25 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. [mp=abstract,
26 heading words, title] (675)
27 or/8-25 (15230)
28 radiculopathy.mp. (290)
29 exp Headache/ or headache.mp. (1709)
30 Temporomandibular joint syndrome/ (67)
31 ((TMJ or TMJD) and pain*).mp. (28)
32 Whiplash injuries/ or whiplash.mp. (594)
33 repetition strain injury/ (312)
34 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi*
35 or myodyn* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (2429)
36 ((back or discogen* or bone or musculoskeletal* or muscle* or skelet* or spinal or spine or vertebra* or joint*
37 or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or
38 cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (12871)
39 36 or/27-35 (17684)
40 37 (acute or emergency or preoperative or postoperative).ti,ab. (12782)
41 38 36 not 37 (16319)
42 39 26 or 38 (25280)
43 40 7 and 39 (532)
44 41 (rat or rats or mouse or mice).ti. (5925)
45 42 animals/ not humans/ (7083)
46 43 exp Rodents/ (8142)
47 44 41 or 42 or 43 (10161)

1
2
3 45 40 not 44 (512)
4 **Central (Cochrane Library via Wiley)**
5 Description:
6 ID Search Hits
7 #1 chronic near/3 pain 9973
8 #2 MeSH descriptor: [Chronic Pain] explode all trees 1178
9 #3 MeSH descriptor: [Osteoarthritis] explode all trees 4754
10 #4 osteoarthrit* 10561
11 #5 osteo-arthritis 69
12 #6 degenerative arthrit* 359
13 #7 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees 4858
14 #8 MeSH descriptor: [Neuralgia] explode all trees 1049
15 #9 MeSH descriptor: [Diabetic Neuropathies] explode all trees 1397
16 #10 neuropath* near/5 (pain* or diabet*) 4465
17 #11 neuralg* 1913
18 #12 zoster 1641
19 #13 MeSH descriptor: [Irritable Bowel Syndrome] explode all trees 674
20 #14 irritable (colon or bowel) 2448
21 #15 IBS 1629
22 #16 MeSH descriptor: [Migraine Disorders] explode all trees 1959
23 #17 migraine 4659
24 #18 MeSH descriptor: [Fibromyalgia] explode all trees 851
25 #19 fibromyalg* 1987
26 #20 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees 238
27 #21 complex regional pain syndromes or causalgia 203
28 #22 MeSH descriptor: [Pain, Intractable] explode all trees 273
29 #23 MeSH descriptor: [Phantom Limb] explode all trees 75
30 #24 MeSH descriptor: [Hyperalgesia] explode all trees 454
31 #25 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) near/3 pain) 2107
32 #26 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 40797
33 #27 MeSH descriptor: [Back Pain] explode all trees 3879
34 #28 MeSH descriptor: [Radiculopathy] explode all trees 303
35 #29 MeSH descriptor: [Musculoskeletal Pain] explode all trees 478
36 #30 MeSH descriptor: [Arthralgia] explode all trees 1313
37 #31 MeSH descriptor: [Headache Disorders] explode all trees 2415
38 #32 MeSH descriptor: [Headache] explode all trees 1798
39 #33 headache* 26942
40 #34 MeSH descriptor: [Temporomandibular Joint Dysfunction Syndrome] explode all trees 179
41 #35 ((TMJ or TMJD) and pain*) 266
42 #36 MeSH descriptor: [Whiplash Injuries] explode all trees 208
43 #37 whiplash 460
44 #38 MeSH descriptor: [Cumulative Trauma Disorders] explode all trees 668
45 #39 backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or
fibromyalgi* or myodyn* or neuralgi* or ischialgi* or crps or rachialgi* 13481
46 #40 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or
joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or
cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) near/3 pain) 28955
47 #41 radiculopathy 893
48 #42 #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41
60275
49 #43 acute or emergency or preoperative or postoperative 200646
50 #44 42 not 43 59058
51 #45 #26 or #44 97623
52 #46 opioid* or opiate* 17932
53 #47 narcotic* 6752

#48 MeSH descriptor: [Analgesics, Opioid] explode all trees 6462
#49 MeSH descriptor: [Narcotics] explode all trees 7246
#50 alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol 32420
#51 adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalge or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydronal or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargin or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinone or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadol or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgc or zydol or zytram 5622
#52 #46 or #47 or #48 or #49 or #50 or #51 42294
#53 #45 and #52 2656

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Search Strategy:

1 Cannabis/ (11443)
2 exp cannabinoids/ or cannabidiol/ or cannabinol/ or dronabinol/ (16399)
3 Endocannabinoids/ (6489)
4 exp Receptors, Cannabinoid/ (10396)
5 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*).mp. (64927)
6 or/1-5 (64927)
7 pain*.mp.jw. or Pain/ (890667)
8 exp Osteoarthritis/ or exp Arthritis, Rheumatoid/ or exp Neuralgia/ or Diabetic Neuropathies/ or Irritable Bowel Syndrome/ or Migraine Disorders/ or Fibromyalgia/ or complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ or Pain, Intractable/ or chronic pain/ or Phantom Limb/ or Hyperalgesia/ or exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ or Radiculopathy/ or musculoskeletal pain/ or headache/ or exp Arthralgia/ or exp Headache Disorders/ or Temporomandibular Joint Dysfunction Syndrome/ or exp whiplash injury/ or exp Cumulative Trauma Disorders/ or exp Peripheral Nervous System Diseases/dt or Pain Measurement/de (423216)
9 ((irrita* or inflam*) adj4 (bowel or colon)).mp. (81237)
10 (osteoartrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*).mp. (827784)
11 Muscle Spasticity/ (9871)
12 Muscle Hypertonia/ (1033)
13 (spasticity or spasm or spastic or hypertonia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word,

1
2
3 protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4 (56343)
5 14 or/7-13 (1660232)
6 15 6 and 14 (6752)
7 16 random:.tw. or placebo:.mp. or double-blind:.tw. (1409704)
8 17 ((treatment or control) adj3 group*).ab. (680082)
9 18 (allocat* adj5 group*).ab. (29935)
10 19 ((clinical or control*) adj3 trial).ti,ab,kw. (333663)
11 20 or/16-19 (1961120)
12 21 randomized controlled trial.pt. (561669)
13 22 controlled clinical trial.pt. (94744)
14 23 clinical trials as topic.sh. (199529)
15 24 randomly.ab. (378041)
16 25 trial.ti. (258476)
17 26 drug therapy.fs. (2458509)
18 27 or/16-26 (4232754)
19 28 15 and 27 (3200)
20 29 animals/ not humans/ (4940789)
21 30 28 not 29 (2513)

EMBASE (OVID)

Search Strategy:

1 cannabis/ (39161)
2 exp cannabinoid/ (76903)
3 medical cannabis/ (3242)
4 exp cannabinoid receptor/ (16300)
5 exp endocannabinoid/ (10122)
6 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (101727)
7 or/1-6 (103167)
8 pain/ or pain*.mp. (1523452)
9 chronic pain/ or exp osteoarthritis/ or exp rheumatoid arthritis/ or exp neuralgia/ or diabetic neuropathy/ or irritable colon/ or exp migraine/ or fibromyalgia/ or intractable pain/ or agnosia/ or exp radiculopathy/ or musculoskeletal pain/ or exp arthralgia/ or headache/ or temporomandibular joint disorder/ or whiplash injury/ or exp cumulative trauma disorder/ (947642)
10 (osteoarthritis* or osteo-arthritis or arthritis* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (1588678)
11 ((irrita* or inflam*) adj4 (bowel or colon)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (143101)
12 muscle hypertonia/ or spasticity/ (29975)
13 (spasticity or spasm or spastic or hypertonia).mp. (102572)
14 or/8-13 (2856349)
15 7 and 14 (15652)
16 clinical article/ (2840832)
17 exp clinical study/ (11038373)

1
2
3 18 clinical trial/ (1030530)
4 19 controlled study/ (8707614)
5 20 randomized controlled trial/ (700351)
6 21 major clinical study/ (4407914)
7 22 double blind procedure/ (193251)
8 23 multicenter study/ (318443)
9 24 single blind procedure/ (45524)
10 25 phase 3 clinical trial/ (59538)
11 26 phase 4 clinical trial/ (4691)
12 27 crossover procedure/ (69709)
13 28 placebo/ (378215)
14 29 or/16-28 (15939371)
15 30 allocat\$.mp. (195320)
16 31 assign\$.mp. (446472)
17 32 blind\$.mp. (548005)
18 33 (clinic\$ adj25 (study or trial)).mp. (7617865)
19 34 compar\$.mp. (9098845)
20 35 control\$.mp. (12329430)
21 36 cross?over.mp. (108597)
22 37 factorial\$.mp. (69675)
23 38 follow?up.mp. (50719)
24 39 placebo\$.mp. (491115)
25 40 prospectiv\$.mp. (1372469)
26 41 random\$.mp. (2010437)
27 42 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).mp. (348231)
28 43 trial.mp. (2377246)
29 44 (versus or vs).mp. (2518554)
30 45 or/30-44 (19623398)
31 46 29 and 45 (12865583)
32 47 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or
33 nonhuman/ (30266244)
34 48 human/ or normal human/ or human cell/ (23473918)
35 49 47 and 48 (23405621)
36 50 47 not 49 (6860623)
37 51 46 not 50 (10162086)
38 52 randomized controlled trial.pt. or randomi?ed.mp. or placebo.mp. (1559060)
39 53 ((treatment or control) adj3 group*).ab. (985064)
40 54 (allocat* adj5 group*).ab. (39102)
41 55 ((clinical or control*) adj3 trial).ti,ab,kw. (472392)
42 56 52 or 53 or 54 or 55 (2453456)
43 57 15 and 51 (5650)
44 58 15 and 56 (2581)
45 59 57 or 58 (6324)

AMED (OVID)

Database: AMED (Allied and Complementary Medicine)

Search Strategy:

1 exp cannabis/ (250)
2 cannabinoids/ (59)
3 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or
hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or
cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or
nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or
sativex or endocannabinoid*).mp. [mp=abstract, heading words, title] (434)
4 or/1-3 (434)

1
2
3 5 pain.mp. or Pain/ (35918)
4 6 exp arthritis rheumatoid/ or exp osteoarthritis/ (5358)
5 7 exp pain/ or neuralgia/ (23893)
6 8 exp diabetic neuropathies/ (1040)
7 9 irritable bowel syndrome/ (199)
8 10 Migraine/ (513)
9 11 fibromyalgia/ or myofascial pain syndromes/ or temporomandibular joint syndrome/ (2280)
10 12 complex regional pain syndromes/ or reflex sympathetic dystrophy/ (197)
11 13 Phantom limb/ (134)
12 14 hyperalgesia/ (74)
13 15 whiplash injuries/ (546)
14 16 repetition strain injury/ (324)
15 17 (osteoarthritis* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or
16 fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or
17 polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or
18 crohn* or colitis* or enteritis* or ileitis*).mp. (18652)
19 18 ((irrita* or inflam*) adj4 (bowel or colon)).mp. (585)
20 19 Muscle spasticity/ (1183)
21 20 Muscle hypertonia/ (84)
22 21 (spasticity or spasm or spastic or hypertonia).mp. [mp=abstract, heading words, title] (2678)
23 22 or/5-21 (50501)
24 23 4 and 22 (118)

25
26 **PsycInfo (OVID)**
27 Database: APA PsycInfo
28 Search Strategy:

29
30 1 exp cannabis/ or exp cannabinoids/ or tetrahydrocannabinol/ (15070)
31 2 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or
32 hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or
33 cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or
34 nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or
35 sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title,
36 tests & measures, mesh word] (30531)
37 3 1 or 2 (30531)
38 4 pain*.mp. or exp PAIN/ (140896)
39 5 (osteoarthritis* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or
40 fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or
41 polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or
42 crohn* or colitis* or enteritis* or ileitis*).mp. [mp=title, abstract, heading word, table of contents, key concepts,
43 original title, tests & measures, mesh word] (74571)
44 6 4 or 5 (180976)
45 7 3 and 6 (2094)
46 8 limit 7 to "therapy (best balance of sensitivity and specificity)" (372)
47 9 (double-blind or random: assigned or control).tw. (522132)
48 10 clinical trials/ (12034)
49 11 (controlled adj3 trial*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title,
50 tests & measures, mesh word] (58491)
51 12 (clinical adj2 trial*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests
52 & measures, mesh word] (50934)
53 13 (randomi?ed adj7 trial*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title,
54 tests & measures, mesh word] (69435)
55 14 or/9-13 (589510)
56 15 7 and 14 (525)
57 16 8 or 15 (525)

- 1
2
3 17 muscle spasms/ (522)
4 18 (spasticity or spasm or spastic or hypertonia).mp. [mp=title, abstract, heading word, table of contents, key
5 concepts, original title, tests & measures, mesh word] (5660)
6 19 17 or 18 (5767)
7 20 3 and 19 (129)
8 21 limit 20 to "therapy (best balance of sensitivity and specificity)" (36)
9 22 14 and 20 (80)
10 23 21 or 22 (80)
11 24 16 or 23 (548)

12
13 Cochrane Library (Wiley)

ID	Search	Hits
#1	MeSH descriptor: [Cannabis] 1 tree(s) exploded	10
#2	MeSH descriptor: [Cannabinoids] explode all trees	928
#3	MeSH descriptor: [Endocannabinoids] explode all trees	63
#4	MeSH descriptor: [Endocannabinoids] explode all trees	63
#5	(Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabiolsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*):ti,ab,kw (Word variations have been searched)	5386
#6	#1 or #2 or #3 or #4 or #5	5386
#7	MeSH descriptor: [Pain] explode all trees	54054
#8	(pain*):ti,ab,kw (Word variations have been searched)	207177
#9	#7 or #8	213544
#10	#6 and #9	794
#11	[mh Osteoarthritis] or [mh ^"Arthritis, Rheumatoid"] or [mh Neuralgia] or [mh ^"Diabetic Neuropathies"] or [mh ^"Irritable Bowel Syndrome"] or [mh ^"Migraine Disorders"] or [mh Fibromyalgia] or [mh ^"complex regional pain syndromes"] or [mh causalgia] or [mh ^"reflex sympathetic dystrophy"] or [mh ^"pain Intractable"] or [mh ^"Phantom Limb"] or [mh Hyperalgesia] or [mh ^"back pain"] or [mh ^"failed back surgery syndrome"] or [mh ^"low back pain"] or [mh Radiculopathy] or [mh ^"musculoskeletal pain"] or [mh headache] or [mh Arthralgia] or [mh ^"Headache Disorders"] or [mh ^"Temporomandibular Joint Dysfunction Syndrome"] or [mh ^"whiplash injury"] or [mh ^"Cumulative Trauma Disorders"] or [mh "Peripheral Nervous System Diseases"/DT] or [mh ^"Pain Measurement"/DE]	35211
#12	(osteoarthrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*)	126119
#13	(irrita* or inflam*) near/4 (bowel or colon)	8688
#14	#11 or #12 or #13136956	
#15	#6 and #14	513
#16	#10 or #15 in Trials	909
#17	MeSH descriptor: [Muscle Spasticity] explode all trees	999
#18	MeSH descriptor: [Muscle Hypertonia] explode all trees	1118
#19	spasticity or spasm or spastic or hypertonia	8777
#20	#17 or #18 or #198841	
#21	#20 and #6	198
#22	#10 or #15 or #21 in Trials	1001

CINAHL (EBSCO)

#	Query	Results
S51	S49 OR S50	849
S50	S48	427
S49	S29 AND S48	721
S48	S4 AND S47	2,847
S47	S7 OR S36 OR S46	580,420
S46	S43 OR S44 OR S45	14,915
S45	TX spasticity or spasm or spastic or hypertonia	14,915
S44	(MH "Muscle Hypertonia")	517
S43	(MH "Muscle Spasticity")	4,382
S42	S31 OR S41	802
S41	S39 OR S40	169
S40	S29 AND S38	154
S39	S38	49
S38	S37 NOT S8	464
S37	S4 AND S36	2,025
S36	S32 OR S33 OR S34 OR S35	458,156
S35	(irrita* or inflam*) N4 (bowel or colon)	18,662
S34	TX (osteoarthrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*)	269,583
S33	(MH Pain+) OR (MH Phantom Limb) OR (MH Hyperalgesia) OR (MH back pain+) OR (MH "failed back surgery syndrome+") OR (MH "low back pain+") OR (MH Radiculopathy) OR (MH "musculoskeletal pain") OR (MH headache) OR (MH Arthralgia+) OR (MH "Headache Disorders+") OR (MH "Temporomandibular Joint Dysfunction Syndrome") OR (MH "whiplash injury+/" or (MH "Cumulative Trauma Disorders+"))	226,279
S32	TX (MH Osteoarthritis+) OR (MH "Arthritis, Rheumatoid+") OR (MH Neuralgia) OR (MH Diabetic Neuropathies) OR (MH "Irritable Bowel Syndrome") OR (MH "Migraine Disorders") OR (MH Fibromyalgia) OR (MH "complex regional pain	85,767

1		
2		
3		
4		syndromes") OR (MH causalgia+) OR (MH "reflex sympathetic
5		dystrophy+)
6	S31	S9 OR S30
7		633
8	S30	S8 AND S29
9		526
10	S29	S16 OR S21 OR S28
11		1,384,715
12	S28	S22 OR S23 OR S24 OR S25 OR S26 OR S27
13		1,181,925
14	S27	(MH "Prospective Studies+")
15		495,834
16	S26	(MH "Evaluation Research+")
17		330,364
18	S25	(MH "Comparative Studies")
19		426,809
20	S24	"latin square"
21		248
22		(MH "Study Design") OR (MH "Crossover Design") OR (MH
23	S23	"Experimental Studies+")
24		423,651
25	S22	(MH "Random Sample+")
26		116,667
27	S21	S17 OR S18 OR S19 OR S20
28		493,219
29	S20	"random*"
30		475,828
31	S19	"placebo*"
32		73,590
33	S18	(MH "Placebos")
34		13,285
35	S17	(MH "Placebo Effect")
36		2,426
37	S16	S10 OR S11 OR S12 OR S13 OR S14 OR S15
38		455,728
39	S15	"triple-blind"
40		489
41	S14	"single-blind"
42		17,122
43	S13	"double-blind"
44		63,811
45	S12	clinical W3 trial
46		278,173
47	S11	"randomi?ed controlled trial*"
48		200,563
49	S10	(MH "Clinical Trials+")
50		333,661
51	S9	S4 AND S7
52		344
53	S8	S4 AND S7
54		2,279
55	S7	S5 OR S6
56		364,720
57	S6	"pain"
58		342,481
59	S5	(MH "Pain+")
60		223,572
54	S4	S1 OR S2 OR S3
55		24,367
56		
57		
58		
59		
60		

1		Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang	
2		or cannador or charas or ganja or ganjah or hashish or hemp or	
3		marihuana or marijuana or nabilone or cesamet or cesametic or	
4		ajulemic acid or cannabichromene or cannabielsoin or	
5		cannabigerol or tetrahydrocannabinol or dronabinol or	
6		levonantradol or nabiximols or palmidrol or	
7		tetrahydronannabinolic acid or tetrahydro cannabinol or marinol	
8	S3	or ttranabinex or sativex or endocannabinoid*	24,367
9			
10	S2	(MH "Medical Marijuana")	2,127
11			
12	S1	(MH "Cannabis")	10,569
13			
14			

PubMed

Search: (((((((((pain* OR spasticity OR spasm OR spastic OR hypertonia OR osteoarthrit* OR osteo-arthritis OR arthrit* OR neuropath* OR neuralgi* OR zoster* OR migraine* OR headache* OR fibromyalgi* OR causalgia OR radiculopathy* OR whiplash OR backache* OR backpain* OR dorsalgi* OR arthralgi* OR polyarthralgi* OR arthrodyni* OR myalgi* OR myodyn* OR ischialgi* OR crps OR brachialgia *or tmj OR tmjd OR IBS OR crohn* OR colitis* OR enteritis* OR ileitis*) AND ((trial* OR random*))) AND ((cannabis OR cannabinol OR cannabinoid* OR cannabidiol OR bhang OR hashish OR hemp OR marihuana OR marijuana OR nabilone OR cesamet OR tetrahydrocannabinol OR dronabinol OR levonantradol OR nabiximols OR palmidrol OR tetrahydronannabinolic OR sativex OR endocannabinoid*)))) AND ((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))) Sort by: Most Recent

Web of Science

10 #8 AND #9 1,871
9 TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*) 5,772,934
8 #7 AND #1 7,146
7 #6 OR #5 OR #4 OR #3 OR #2 1,648,139
6 TS=(spasticity or spasm or spastic or hypertonia) 50,631
5 TS= tmj OR TS= tmjd OR TS= IBS OR TS= crohn* OR TS= colitis* OR TS= enteritis* OR TS= ileitis* 185,102
4 TS= arthrodyni* OR TS= myalgi* OR TS= myodyn* OR TS= ischialgi* OR TS= crps OR TS= brachialgia 13,911
3 TS= headache* OR TS= fibromyalgi* OR TS= causalgia OR TS= radiculopathy* OR TS= whiplash OR TS= backache* OR TS= backpain* OR TS= dorsalgi* OR TS= arthralgi* OR TS= polyarthralgi* 129,034
2 TS= pain* OR TS= osteoarthrit* OR TS= osteo-arthritis OR TS= arthrit* OR TS= neuropath* OR TS= neuralgi* OR TS= zoster* OR TS= migraine* 1,373,602
1 TS=cannabis OR TS=cannabinol OR TS=cannabinoid* OR TS=cannabidiol OR TS=bhang OR TS=hashish OR TS=hemp OR TS=marihuana OR TS=marijuana OR TS=nabilone OR TS=cesamet OR TS=tetrahydrocannabinol OR TS=dronabinol OR TS=levonantradol OR TS=nabiximols OR TS=palmidrol OR TS=tetrahydronannabinolic OR TS=sativex OR TS=endocannabinoid* 82,113

Cannabis-Med

International Association for Cannabinoid Medicines, database of clinical studies

<http://www.cannabis-med.org/studies/study.php>

Diagnosis: Pain or spasticity

AND

Study design: Controlled Study

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4 Cannabinoids for chronic non-cancer pain (matrix of evidence)
5 <https://www.epistemonikos.org/en/matrixes/58f5158d7aac87666ca8853>
6 97 Primary Studies
7 Cannabis Spasticity
8 45 Primary studies
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For peer review only

eAppendix 2: Full reference list of eligible studies

(Studies reported 2 separate trials in one paper: Arai et al. 2015, and Tominaga et al 2016.)

1. Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of Tapentadol extended release compared
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For peer review only

eAppendix 3: Reference list of studies excluded from quantitative analysis

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eTable 1. Baseline characteristics of eligible randomized controlled trials (N = 90 RCTs)

Author	Total # randomized	Pain condition	Age (year)	Sex (female%)	Duration of chronic pain(month)	# of arms	Interventions	Control	Length of follow-up (days)
Opioids versus placebo									
Afilalo (2010)	1030	Osteoarthritis	58	61	NR	3	Tapentadol-ER Oxycodone-ER	Placebo	84
Arai (2015)	150	Mixed neuropathic & non-neuropathic conditions	66	67	NR	2	Fentanyl-PATCH	Placebo	84
Arai (2015)	163	Mixed neuropathic	66	49	NR	2	Fentanyl-PATCH	Placebo	84
Babul (2004)	246	Osteoarthritis	61	61	154	2	Tramadol-ER	Placebo	84
Boureau (2003)	127	Postherpetic neuralgia	66	62	6.7	2	Tramadol-ER	Placebo	42
Breivik (2010)	199	Osteoarthritis	50	58	NR	2	Buprenorphine-PATCH	Placebo	180
Burch (2007)	646	Osteoarthritis	62	63	NR	2	Tramadol-ER	Placebo	84
Buynak (2010)	981	Low back pain	50	58	NR	3	Tapentadol-ER; Oxycodone-ER	Placebo	105
Caldwell (2002)	295	Osteoarthritis	61	62	NR	4	Morphine-ER	Placebo	28
Caldwell (1999)	70	Osteoarthritis	57	53	NR	3	Oxycodone-ER	Placebo	28
Christoph (2017)	252	neuropathic & non-neuropathic conditions		62	NR	5	Tapentadol-ER	Placebo	98
Chu (2012)	139	Low back pain	45	44	NR	2	Morphine-ER	Placebo	30
DeLemos (2011)	808	Osteoarthritis	60	100	96.7	2	Tramadol-ER	Placebo	84
Fishman (2007)	552	Osteoarthritis	61	62	NR	4	Tramadol-ER	Placebo	84
Fleischmann (2001)	129	Osteoarthritis	62	62	364	2	Tramadol-NR	Placebo	91
Friedmann (2011)	412	Osteoarthritis	58	70	NR	2	Oxycodone-ER	Placebo	84
Gana (2006)	1020	Osteoarthritis	58	62	NR	5	Tramadol-ER	Placebo	84
Gilron (2005)	57	Postherpetic neuralgia & painful diabetic neuropathy	50	56	NR	2	Morphine-ER	Placebo	28
Gimbel (2003)	159	Painful diabetic neuropathy			54.5	2	Oxycodone-ER	Placebo	42
Gimbel (2016)	511	Low back pain	59	48	NR	2	Buprenorphine-Buccal	Placebo	84
Gordon (2010)	78	Low back pain	54	47	NR	2	Buprenorphine-PATCH	Placebo	28
Gordon (2010)	79	Mixed neuropathic & non-neuropathic conditions	50	60	170	2	Buprenorphine-PATCH	Placebo	28

Hale (2007)	143	Low back pain	56	55	NR	2	Oxymorphone-ER	Placebo	84
Hale (2010)	268	Low back pain	48	50	NR	2	Hydromorphone-ER	Placebo	84
Hale (2015)	370	Low back pain	51	51	NR	2	Hydrocodone-ER	Placebo	84
Harati (1998)	131	Painful diabetic neuropathy	59	40	NR	2	Tramadol-NR	Placebo	42
Huse (2001)	12	Phantom limb pain	51	17	NR	2	Morphine-ER	Placebo	28
Katz (2007)	205	Low back pain	49	53	NR	2	Oxymorphone-ER	Placebo	84
Katz (2015)	389	Low back pain	49	53	NR	2	Oxycodone-ER	Placebo	84
Khoromi (2007)	55	Lumbar radiculopathy			NR	2	Morphine-ER	Placebo	49
Kawamata (2019)	130	Low back pain	53	45	NR	2	Oxycodone-ER	Placebo	49
Langford (2006)	399	Osteoarthritis	63	67	NR	2	Fentanyl-PATCH	Placebo	42
Lin (2016)	21	Low back pain	41.9	33	97.2	2	Morphine-ER	Placebo	30
Ma (2008)	116	Chronic neck pain	56	38	NR	2	Oxycodone-ER	Placebo	28
Markenson (2005)	107	Osteoarthritis	63	38	NR	2	Oxycodone-ER	Placebo	90
Matsumoto (2005)	491	Osteoarthritis	63	62	NR	4	Oxymorphone-ER Oxycodone-ER	Placebo	28
Mayorga (2016)	98	Osteoarthritis	59	56	NR	4	Oxycodone-ER	Placebo	112
Moran (1991)	15	Osteoarthritis		5	NR	2	Morphine-ER	Placebo	28
Moulin (1996)	61	Chronic post-traumatic pain	40	59	40.8	2	Morphine-ER	Placebo	77
Munera (2010)	315	Osteoarthritis	61	67	NR	2	Buprenorphine-PATCH	Placebo	28
Niesters (2014)	25	Painful diabetic neuropathy	63	41.6	NR	2	Tapentadol-ER	Placebo	28
Norrbrink (2009)	36	Post-traumatic neuralgia	51	78	NR	2	Tramadol-NR	Placebo	28
Peloso (2000)	103	Osteoarthritis	62	40	NR	2	Codeine-ER	Placebo	28
Raja (2002)	76	Postherpetic neuralgia			NR	2	Morphine-ER	Placebo	56
Rauck (2013)	990	Osteoarthritis	50	56	NR	3	Hydromorphone-ER	Placebo	84
Rauck (2014)	302	Low back pain	50	63	NR	2	Hydrocodone-ER	Placebo	84
Rauck (2016)	420	Low back pain	59	64	NR	2	Buprenorphine-Buccal	Placebo	84
Russell (2000)	69	Fibromyalgia	49	94	NR	2	Tramadol-ER	Placebo	42
Schnitzer (2000)	254	Low back pain	47	50	NR	2	Tramadol-NR	Placebo	28
Schwartz (2011)	395	Painful diabetic neuropathy	62	43	76	2	Tapentadol-ER	Placebo	84

1	Serrie (2017)	990	Osteoarthritis	62	69	NR	3	Tapentadol-ER Oxycodone-ER	Placebo	105
2	Simpson (2016)	186	Diabetic neuropathy	63	33	NR	2	Buprenorphine-PATCH	Placebo	84
3	Sindrup (1999)		Painful diabetic neuropathy	57	24	36		Tramadol-ER	Placebo	28
4	Sindrup (2012)	64	Painful polyneuropathy			NR	3	Tramadol-ER	Placebo	28
5	Steiner (2011)	541	Low back pain	49	55	108.6	2	Buprenorphine-PATCH	Placebo	84
6	Thorne (2008)	100	Osteoarthritis	61	55	NR	2	Tramadol-ER	Placebo	28
7	Tominaga (2016)	91	neuropathic & non-neuropathic conditions			NR	2	Tapentadol-ER	Placebo	84
8	Tominaga (2016)	91	Postherpetic neuralgia & painful diabetic neuropathy			NR	2	Tapentadol-ER	Placebo	84
9	Uberall (2012)	240	Low back pain			NR	2	Tramadol-ER	Placebo	28
10	Vinik (2014)	320	Painful diabetic neuropathy	58	41	NR	2	Tapentadol-ER	Placebo	84
11	Vojtassak (2011)	288	Osteoarthritis	66	72	NR	2	Hydromorphone-ER	Placebo	112
12	Vorsanger (2008)	386	Low back pain	47	50	NR	3	Tramadol-ER	Placebo	84
13	Watson (1998)	50	Postherpetic neuralgia	70	44	31	2	Oxycodone-ER	placebo	28
14	Webster (2006)	307	Low back pain	48	61	NR	4	Oxycodone-ER	Placebo	84
15	Wen (2015)	588	Low back pain	48	57	NR	2	Hydrocodone	Placebo	84
16	Wu (2008)	60	postamputation	63	21	51.3	2	Morphine-ER	Placebo	42
17	Opioids versus medical cannabis									
18	Frank 2008	192	Neuropathic pain	50	26	76.4	2	THC	Dihydrocodeine	42
19	Medical cannabis versus placebo									
20	Andresen (2016)	73	Spinal cord injury-related neuropathic pain	56	26	≥3	2	PEA	Placebo	84
21	Blake (2006)	58	Rheumatoid arthritis pain	63	79	NR	2	THC/CBD	Placebo	48
22	de Vries (2017)	65	Chronic abdominal pain	53	39	≥3	2	THC	Placebo	51
23	Eibach (2020)	68	HIV associated neuropathic pain	50	6	157.2	2	Cannabidiol (CBDV)	Placebo	28
24	Germini (2017)	20	Mixed chronic noncancer pain	83	100	≥6	2	PEA	Placebo	42
25	Hunter (2018)	320	Osteoarthritis	62	51	≥12	2	CBD	Placebo	84
26	Langford (2013)	339	Multiple sclerosis central pain	49	68	65.5	2	THC/CBD	Placebo	98
27	Markova (2018)	106	Multiple sclerosis with pain (no details about pain condition)	51.3	80	170.4	2	THC/CBD	Placebo	84

NCT00710424 (2006)	297	Diabetic neuropathy	60	38	≥ 6	2	THC/CBD	Placebo	98
Novotna (2011)	241	Multiple sclerosis with pain (no details about pain condition)	49	60	151.2	2	THC/CBD	Placebo	84
Nurmikko (2007)	125	Peripheral neuropathic pain	53	59	75.6	2	THC/CBD	Placebo	35
Pinsger (2006)	60	Refractory pain related to musculoskeletal system	55	77	240	2	THC	Placebo	30
Rog (2005)	66	Multiple sclerosis central pain	49	79	138.8	2	THC/CBD	Placebo	28
Schimrigk (2017)	240	Multiple sclerosis central pain	48	73	NR	2	THC	Placebo	112
Selvarajah (2010)	30	Diabetic neuropathy	56	37	NR	2	THC/CBD	Placebo	84
Serpell (2014)	246	Peripheral neuropathy	57	61	75.6	2	THC/CBD	Placebo	98
Skrabek (2008)	40	Fibromyalgia	49	NR	NR	2	THC	Placebo	28
Toth (2012)	26	Diabetic neuropathy	61	46	85.8	2	THC	Placebo	35
van Amerongen (2018)	24	Multiple sclerosis neuropathic pain and spasticity	54	6	137.4	2	THC	Placebo	28
Wissel (2006)	26	Chronic upper motor neuron syndrome	44.8	69	NR	2	THC	Placebo	28
Xu (2020)	29	Peripheral neuropathic pain	68	38	≥ 3	2	CBD	Placebo	28
Zajicek (2003 and 2005)	657	Multiple sclerosis with pain (no details about pain condition)	51	63	NR	2	THC/CBD	Placebo	112
Zajicek (2012)	279	Multiple sclerosis with pain (no details about pain condition)	52	63	NR	2	THC/CBD	Placebo	84

eTable 2. Risk of bias assessment of the eligible randomized controlled trials (N = 90 RCTs)

Study	Loss to follow-up (%)	Randomization	Concealment	Blinding of patients	Blinding of care providers	Blinding of data collectors	Blinding of outcome assessors
Afilalo 2010	51	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Andresen 2016	15	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Arai 2015a	49	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Arai 2015b	54	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Babul 2004	50	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Blake 2006	7	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Boureau 2003	15	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Breivik 2010	44	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Burch 2007	24	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Buynak 2010	53	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Caldwell 1999	34	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Caldwell 2002	38	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Christoph 2017	30	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Chu 2012	26	inadequate randomization	inadequate allocation concealment	Yes	No	Yes	Yes
de Vries 2017	25	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
DeLemos 2011	48	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Eibach 2020	18	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Fishman 2007	44	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Fleischmann 2001	71	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Frank 2008	24	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Friedmann 2011	36	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Gana 2006	45	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes

Germini 2017	30	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Gilron 2005	9	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Gimbel 2003	28	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Gimbel 2016	31	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Gordon 2010a	35	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Gordon 2010b	37	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Hale 2007	53	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Hale 2010	59	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Hale 2015	20	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Harati 1998	37	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Hunter 2018	26	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Huse 2001	17	inadequate randomization	inadequate allocation concealment	No	No	No	No
Katz 2007	42	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Katz 2015	43	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Kawamata 2019	37	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Khoromi 2007	33	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Langford 2006	52	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Langford 2013	12	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Lin 2016	0	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Ma 2008	90	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Markenson 2005	66	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Markova 2018	9	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Matsumoto 2005	45	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Mayorga 2016	61	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Moran 1991	25	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes

Moulin 1996	25	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Munera 2010	51	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
NCT00710424 2006	23	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Niesters 2014	0	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Norrbrink 2009	36	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Novotna 2011	7	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Nurmikko 2007	16	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Peloso 2000	36	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Pinsger 2006	30	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Raja 2002	42	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Rauck 2013	51	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	No
Rauck 2014	39	inadequate randomization	adequate allocation concealment	Yes	Yes	No	No
Rauck 2016	9	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Rog 2005	3	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Russell 2000	1	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Schimrigk 2017	26	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Schnitzer 2000	43	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Schwartz 2011	33	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Selvarajah 2010	20	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Serpell 2014	30	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Serrie 2017	46	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Simpson 2016	33	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Sindrup 1999	20	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Sindrup 2012	8	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Skrabek 2008	18	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes

Steiner 2011	32	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Thorne 2008	25	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Tominaga 2016a	13	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Tominaga 2016b	9	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Toth 2012	4	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Uberall 2012	25	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
van Amerongen 2018	4	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Vinik 2014	29	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Vojtassak 2011	31	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Vorsanger 2008	38	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Watson 1998	22	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Webster 2006	54	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Wen 2015	25	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Wissel 2006	15	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Wu 2008	41	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Xu 2020	21	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Zajicek 2003 & 2005	4	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Zajicek 2012	20	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes

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3 **eTable 3. Network estimates and their certainty in evidence (GRADE) evaluating the effects of opioid and**
4 **cannabis therapy in patients with chronic non-cancer pain across different outcomes**

5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 Outcome	Comparison	Direct Estimate MD (95% CI)	Indirect Estimate MD (95% CI)	Network Estimate* MD (95% CrI))	GRADE
8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 Pain (VAS 0-10)	Opioid vs placebo	-0.84 (-0.99, -0.69)	-0.83 (-0.97, -0.70)	-0.83 (-0.97, -0.70)	Moderate ²
	Medical cannabis vs placebo	-0.63 (-0.94, -0.32)	-0.59 (-0.88, -0.32)	-0.60 (-0.87, -0.33)	Low ^{2,8}
	Medical cannabis vs opioid	0.13 (-0.54, 0.80)	0.24 (-0.07, 0.55)	0.23 (-0.06, 0.53)	Low ^{1,8}
12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 Physical function (SF 0-100)	Opioid vs placebo	2.38 (1.05, 3.72)	–	2.05 (1.01, 3.29)	Moderate ⁸
	Medical cannabis vs placebo	3.00 (0.08, 5.91)	–	2.52 (0.37, 4.91)	Moderate ⁸
	Medical cannabis vs opioid	–	0.47 (-1.97, 2.99)	0.47 (-1.97, 2.99)	Moderate ²
16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 Emotional function (SF 0-100)	Opioid vs placebo	-0.00 (-1.09, 1.09)	–	-0.15 (-1.10, 0.92)	High
	Medical cannabis vs placebo	0.72 (-1.01, 2.45)	–	0.70 (-1.42, 2.84)	Moderate ⁸
	Medical cannabis vs opioid	–	0.85 (-1.55, 3.18)	0.85 (-1.55, 3.18)	Low ^{2,8}
20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 Role function (SF 0-100)	Opioid vs placebo	0.91 (-1.17, 2.98)	–	0.94 (-1.26, 3.17)	Moderate ⁸
	Medical cannabis vs placebo	1.27 (-12.39, 14.93)	–	0.88 (-3.78, 6.05)	Moderate ⁸
	Medical cannabis vs opioid	–	-0.05 (-5.16, 5.60)	-0.05 (-5.16, 5.60)	Moderate ⁸
24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 Social function (SF 0-100)	Opioid vs placebo	0.47 (-1.47, 2.41)	–	1.17 (-1.72, 4.58)	Moderate ⁸
	Medical cannabis vs placebo	-1.82 (-5.79, 2.15)	–	1.70 (-3.28, 8.13)	Moderate ⁸
	Medical cannabis vs opioid	–	0.55 (-5.34, 7.41)	0.55 (-5.34, 7.41)	Moderate ⁸
28 29 30 31 32 33 34 35 36 37 38 39 40 Sleep quality (0-100)	Opioid vs placebo	5.55 (2.67, 8.43)	–	5.46 (2.62, 8.59)	Moderate ²
	Medical cannabis vs placebo	6.04 (1.43, 10.66)	–	5.95 (1.82, 10.24)	Low ^{2,8}
	Medical cannabis vs opioid	–	0.49 (-4.72, 5.59)	0.49 (-4.72, 5.59)	Low ^{2,8}
32 33 34 35 36 37 38 39 40 Outcome	Comparison	Direct Estimate OR (95% CI)	Indirect Estimate OR (95% CI)	Network Estimate* OR (95% CI)	GRADE
33 34 35 36 37 38 39 40 Discontinuations due to adverse events (enriched)	Opioid vs placebo	1.39 (1.04, 1.86)	–	1.25 (0.91, 1.67)	Low ^{1,8}
	Medical cannabis vs placebo	5.00 (0.25, 101.7)	–	0.96 (0.09, 10.80)	Low ^{1,8}
	Medical cannabis vs opioid	–	0.77 (0.07, 8.83)	0.77 (0.07, 8.83)	Low ^{1,8}
37 38 39 40 Discontinuations due to adverse events (non-enriched)	Opioid vs placebo	3.58 (3.00, 4.27)	3.27 (2.70, 3.93)	3.27 (2.71, 3.90)	Moderate ¹
	Medical cannabis vs placebo	2.47 (1.49, 4.11)	1.78 (1.15, 2.63)	1.80 (1.19, 2.63)	High
	Medical cannabis vs opioid	0.50 (0.16, 1.61)	0.54 (0.34, 0.84)	0.55 (0.36, 0.83)	Moderate ¹

* Imprecision only incorporated at network level not at direct or indirect.

Abbreviations: MD: Mean difference; 95 CI%: 95% Confidence Intervals; GRADE Certainty of Evidence.

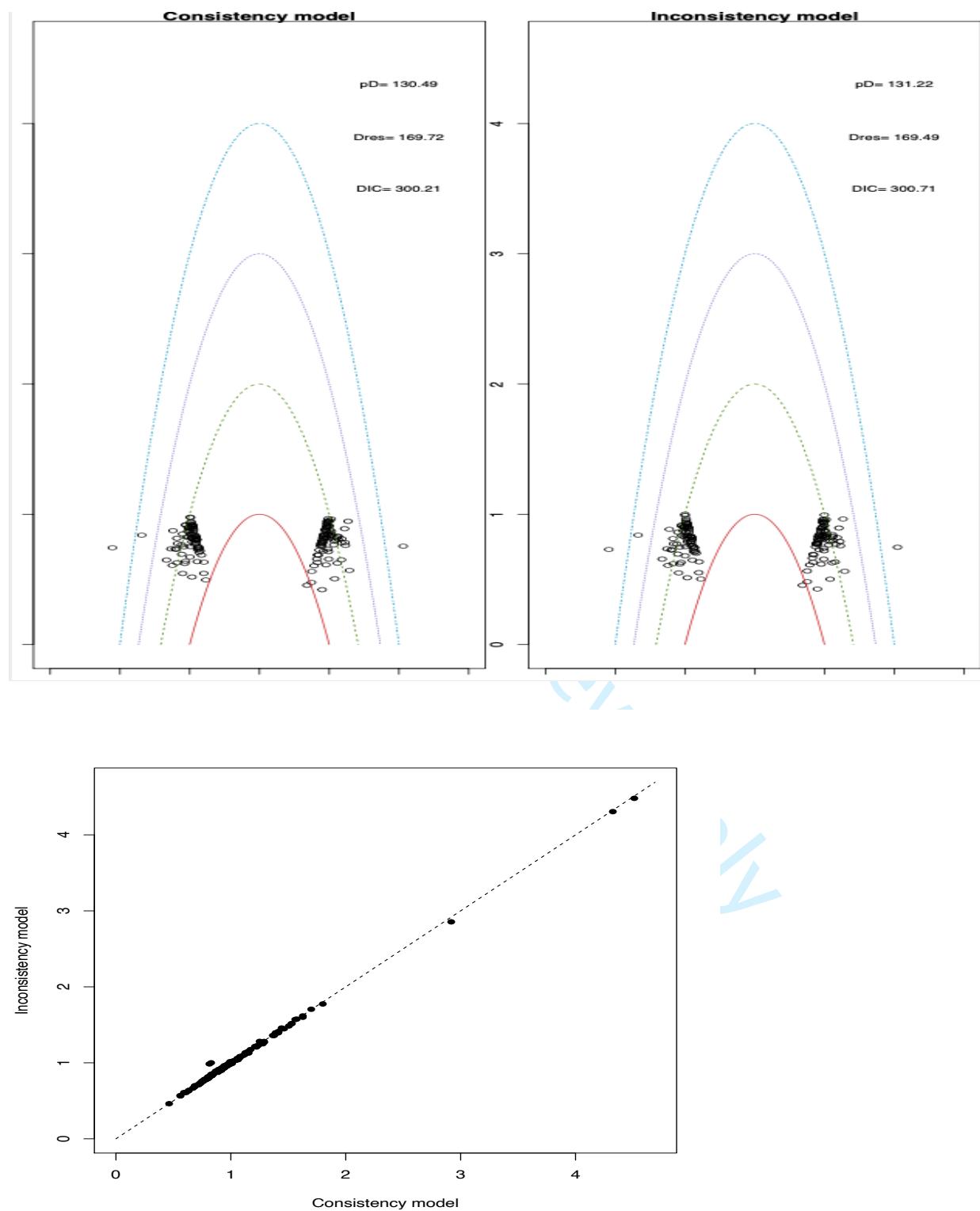
GRADE Assessment: Reasons for downgrading direct evidence:

1. Rated down due to risk of bias
2. Rated down due to inconsistency
3. Rated down due to imprecision (effects were rated down if the associated measure of precision included no effect [a mean difference of 0])
4. Rated down due to indirectness
5. Rated down due to publication bias

Reasons for downgrading indirect evidence:

6. Rated down for intransitivity
 7. Rated down due to incoherence
 8. Rated down due to imprecision (either due to inclusion of the null value in the 95%CI, or because the evidence is provided by a small number of patients – a total number of patients less than the optimal information size [n=300])
- When two of the same superscripts are listed with an estimate of treatment effect (e.g. ^{1,1}), this means the certainty of evidence (GRADE) was downgraded for 2 levels (-2), instead of one (-1)

5
6
eFigure 1. Pain, random effects consistency and inconsistency model

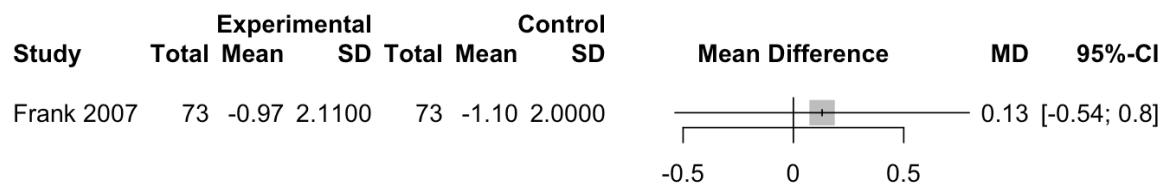


eTable 4. Pain, node splitting outputs

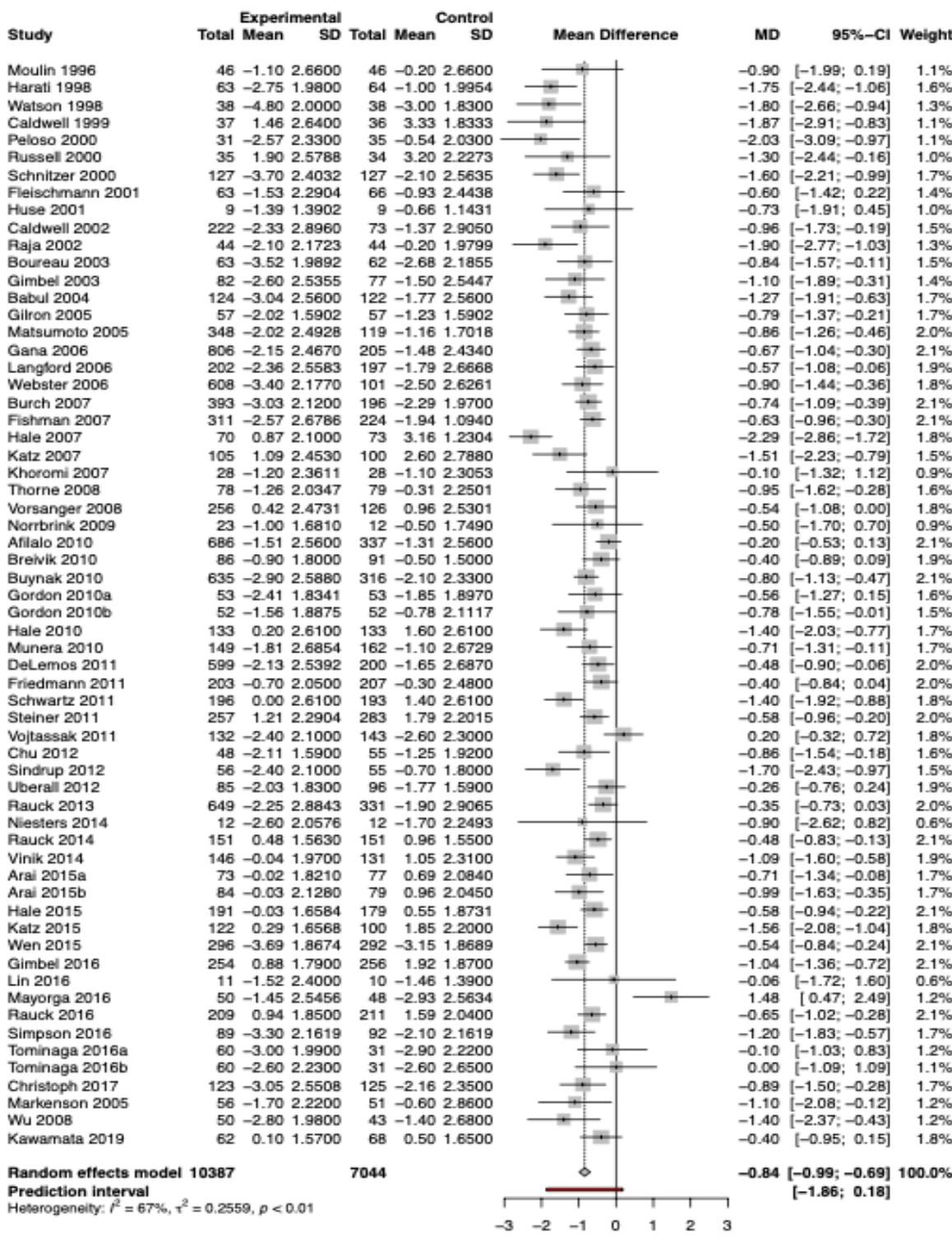
Comparison of direct versus indirect evidence - Mean change in pain VAS from baseline

Comparisons	Direct evidence	Indirect evidence
Medical cannabis vs. Opioids	0.13 (-0.54, 0.80)	0.23 (-0.10, 0.55)

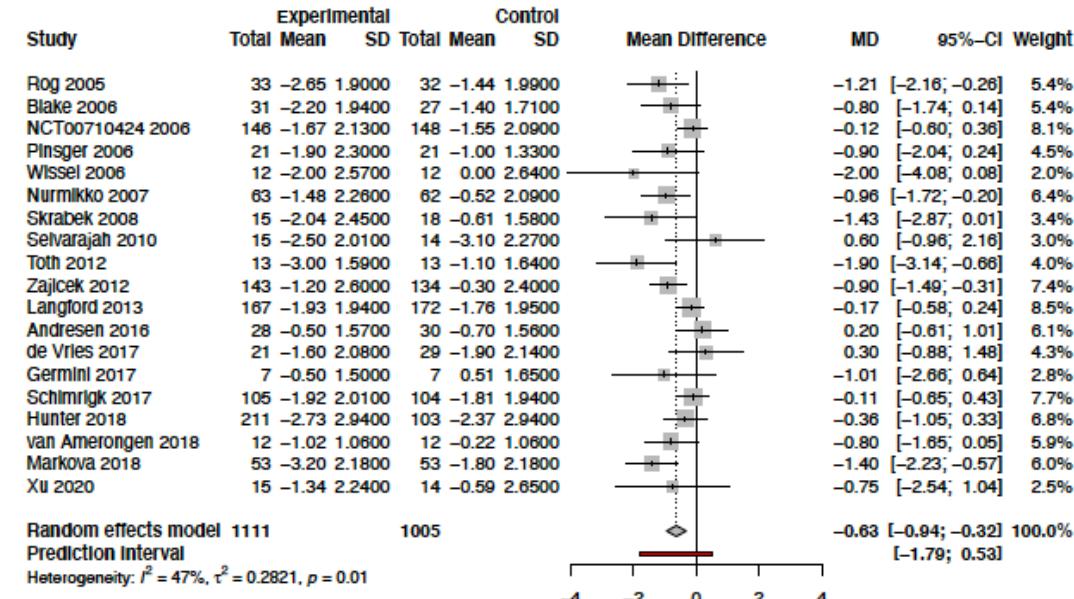
P-value = 0.792

Direct evidence forest plot

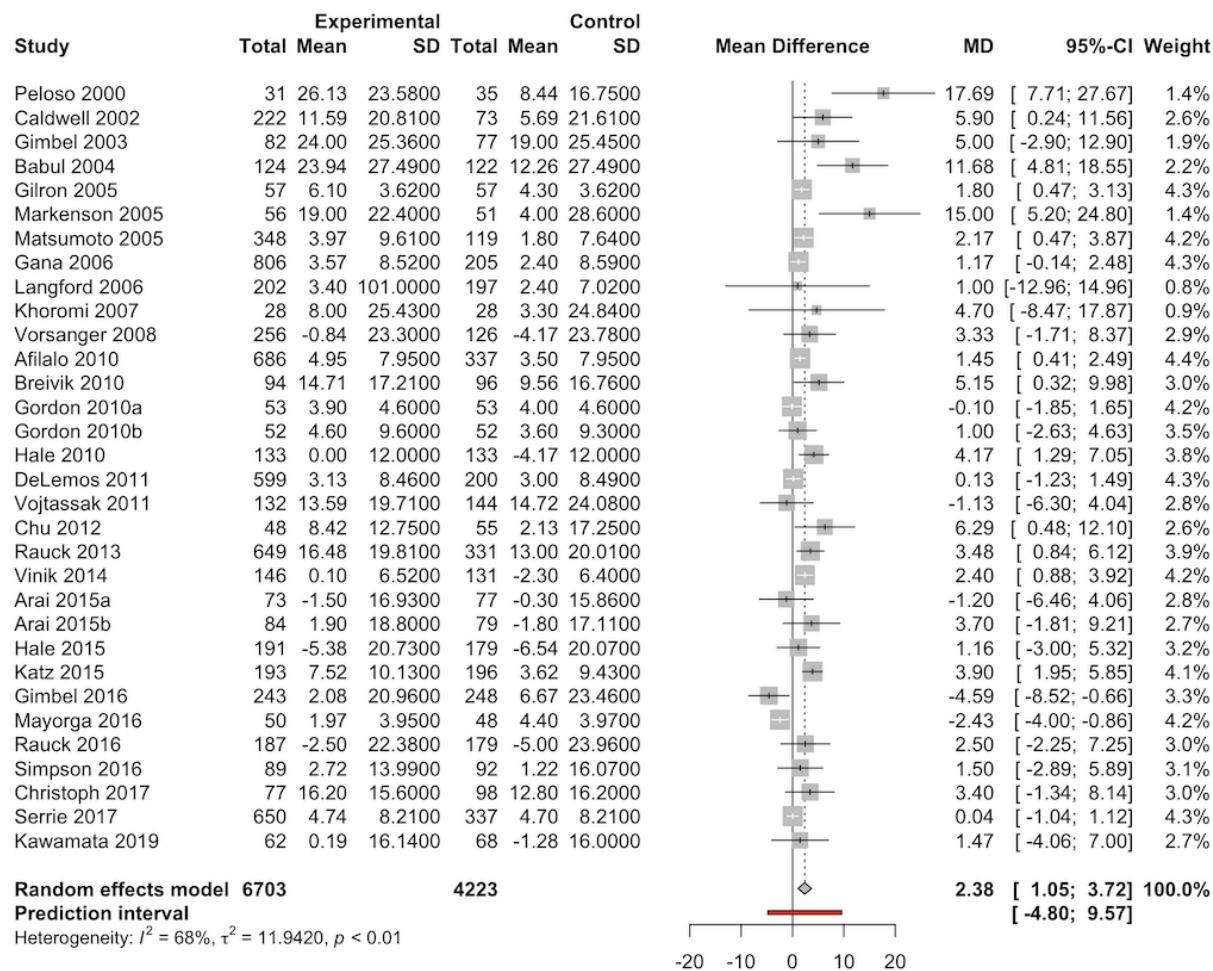
eFigure 2. Pain, opioids versus placebo pairwise meta-analysis random effect model



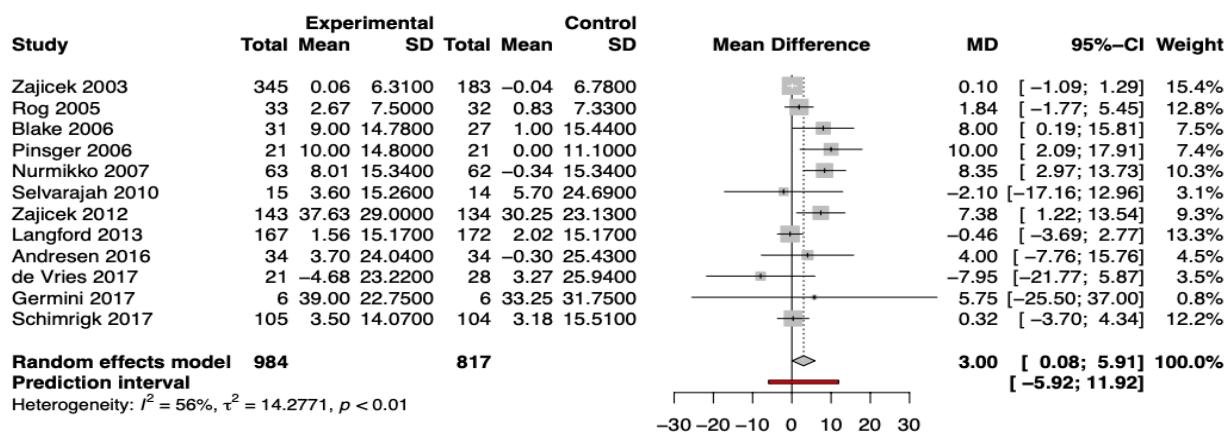
eFigure 3. Pain, medical cannabis versus placebo pairwise meta-analysis random effects model



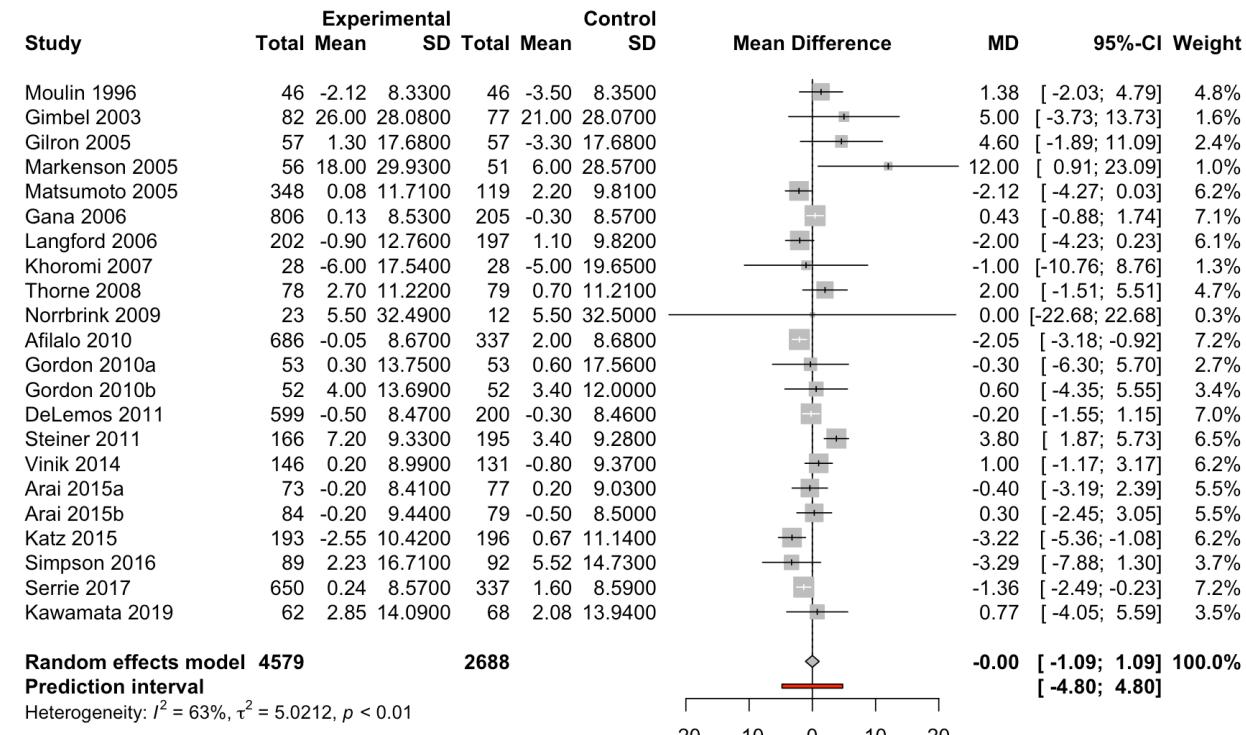
eFigure 4. Physical functioning, opioids versus placebo pairwise meta-analysis random effect model



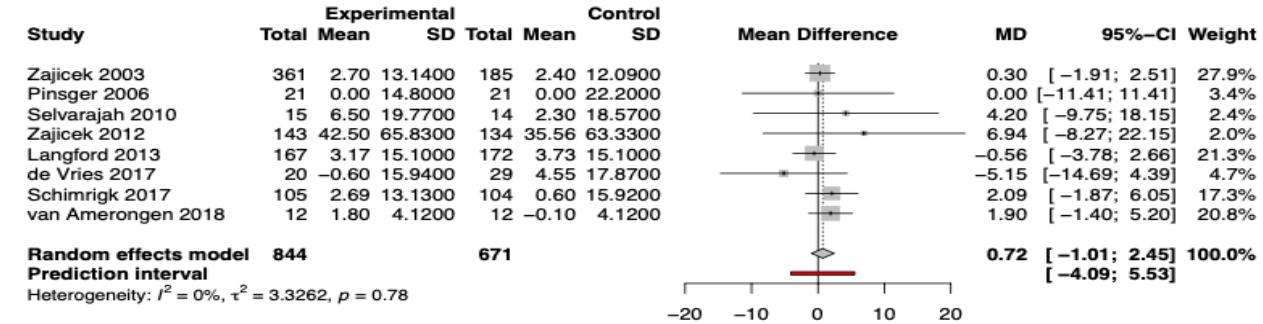
eFigure 5. Physical functioning, medical cannabis versus placebo pairwise meta-analysis random effect model



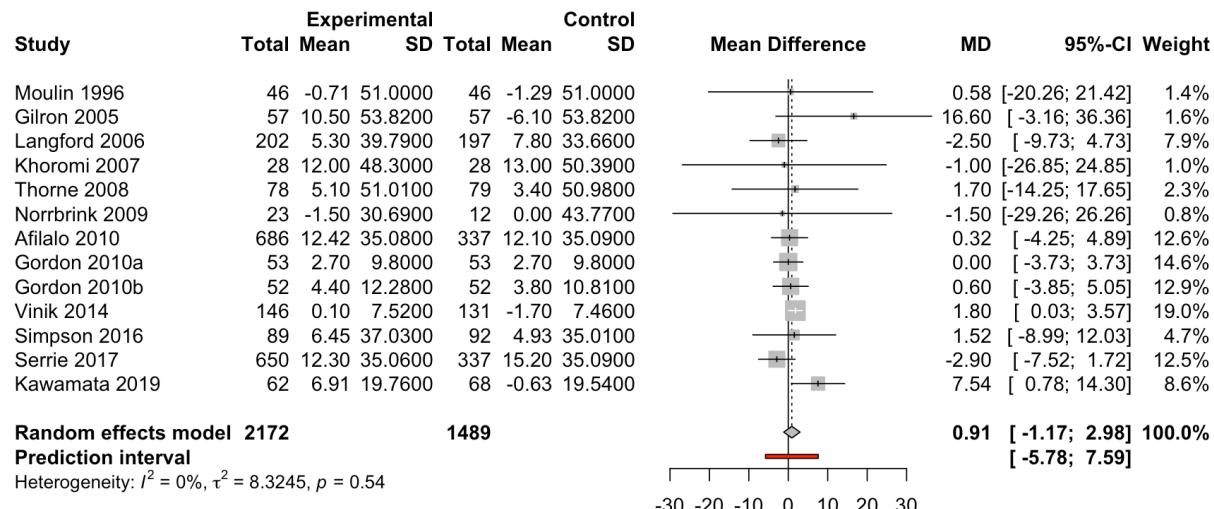
eFigure 6. Emotional functioning, opioids versus placebo pairwise meta-analysis random effect model



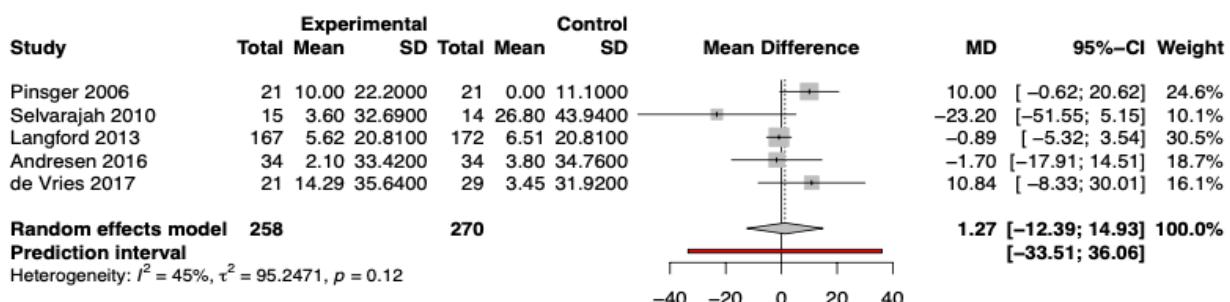
eFigure 7. Emotional functioning, medical cannabis versus placebo pairwise meta-analysis random effect model



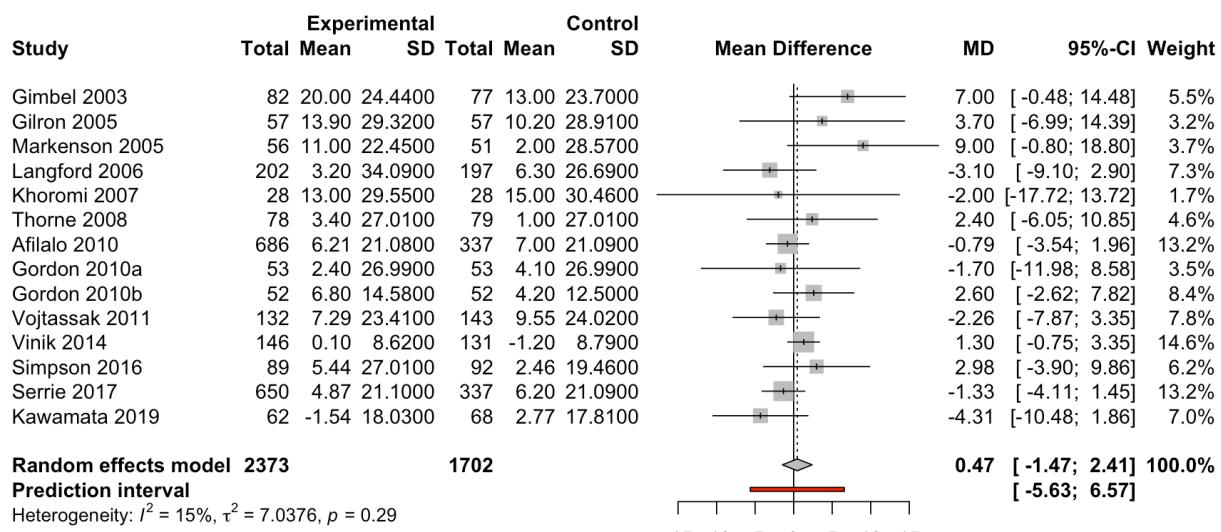
eFigure 8. Role functioning, opioids versus placebo pairwise meta-analysis random effect model



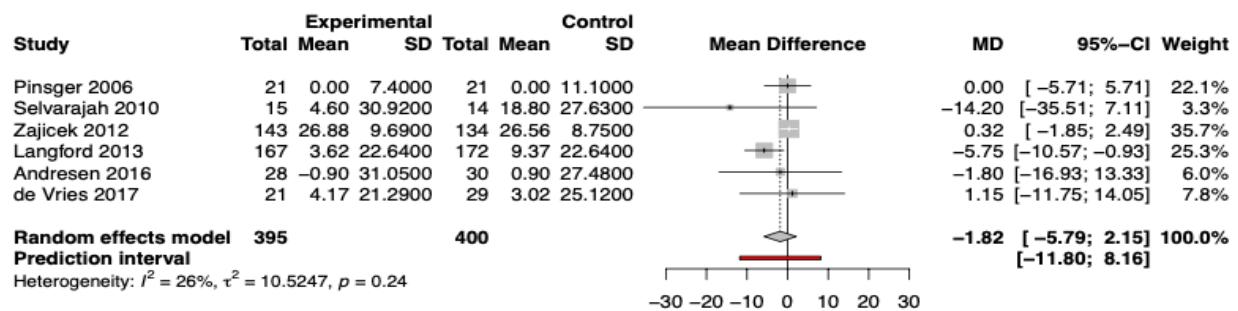
eFigure 9. Role functioning, medical cannabis versus placebo pairwise meta-analysis random effect model



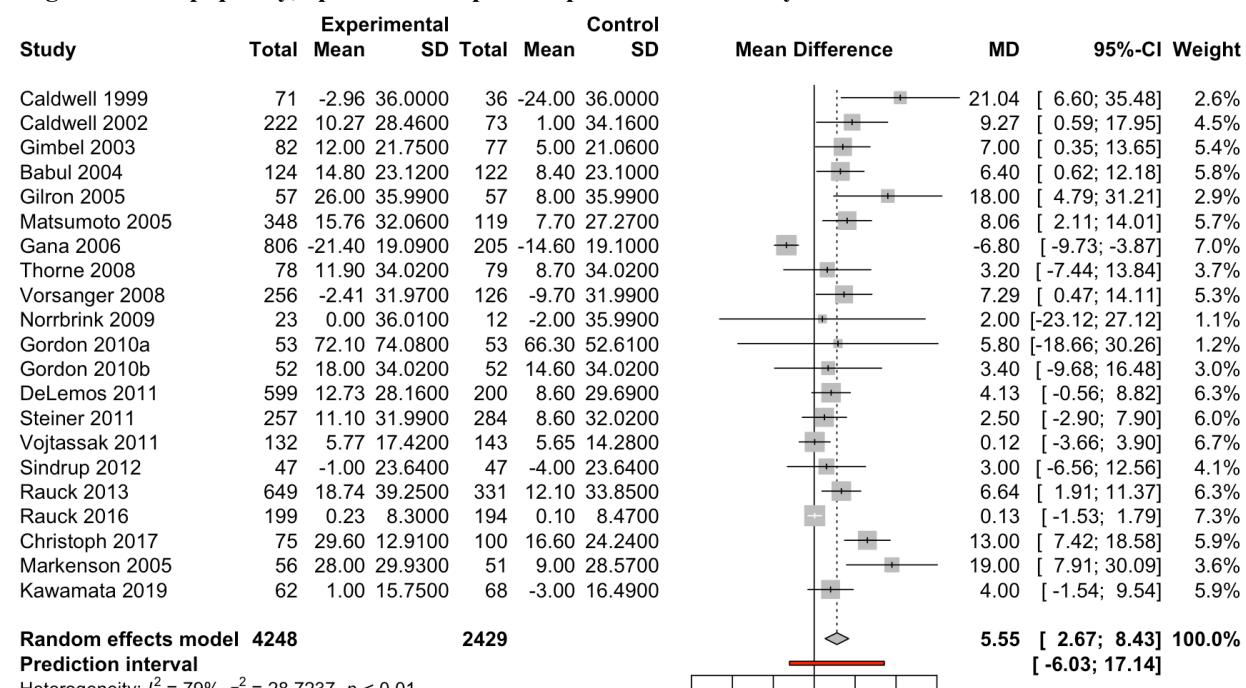
eFigure 10. Social functioning, opioids versus placebo pairwise meta-analysis random effect model



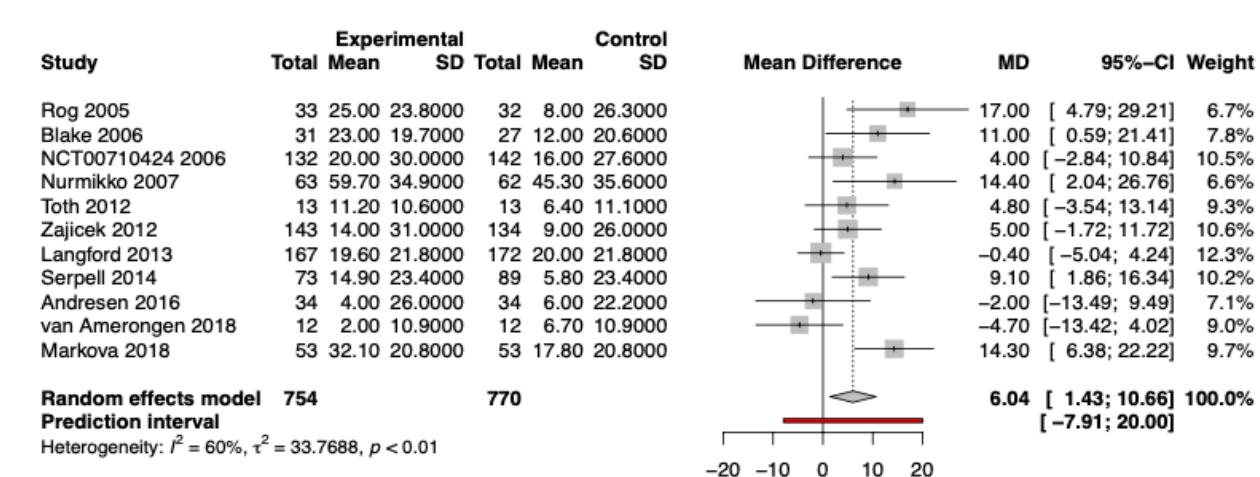
eFigure 11. Social functioning, medical cannabis versus placebo pairwise meta-analysis random effect model



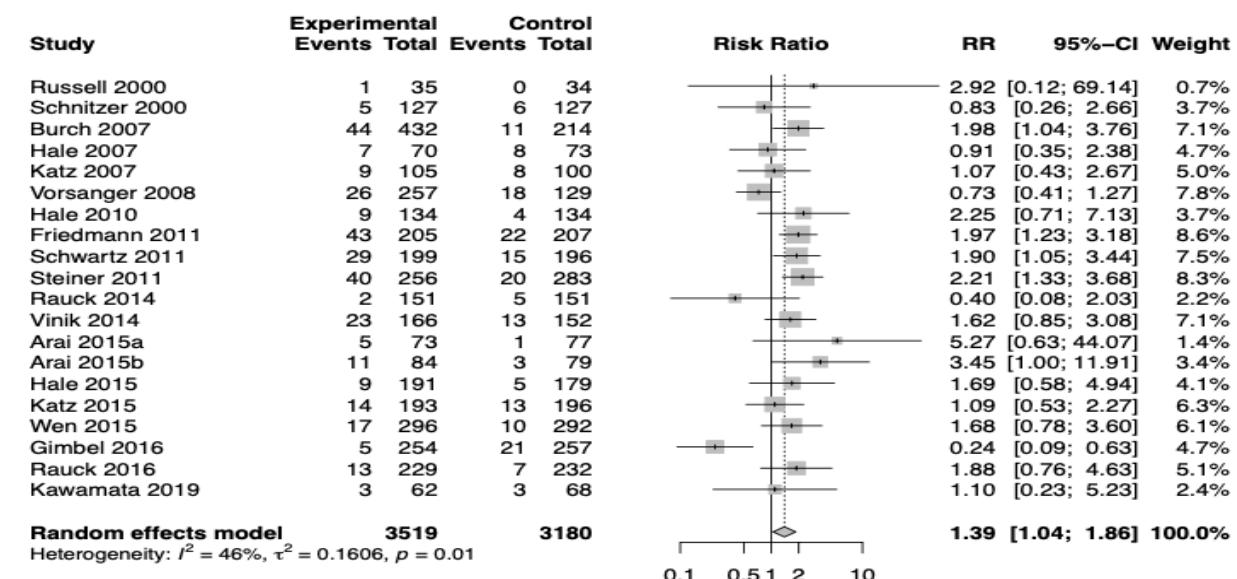
eFigure 12. Sleep quality, opioids versus placebo pairwise meta-analysis random effect model



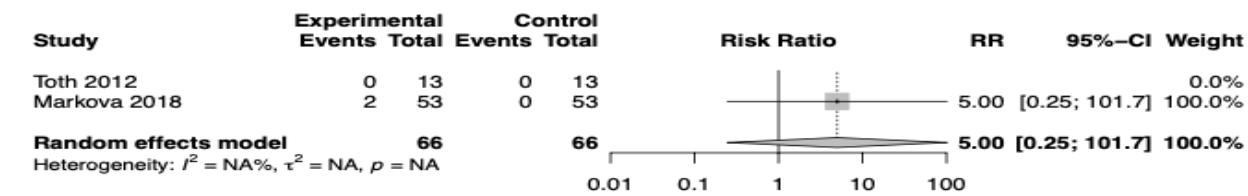
eFigure 13. Sleep quality, medical cannabis versus placebo pairwise meta-analysis random effect model



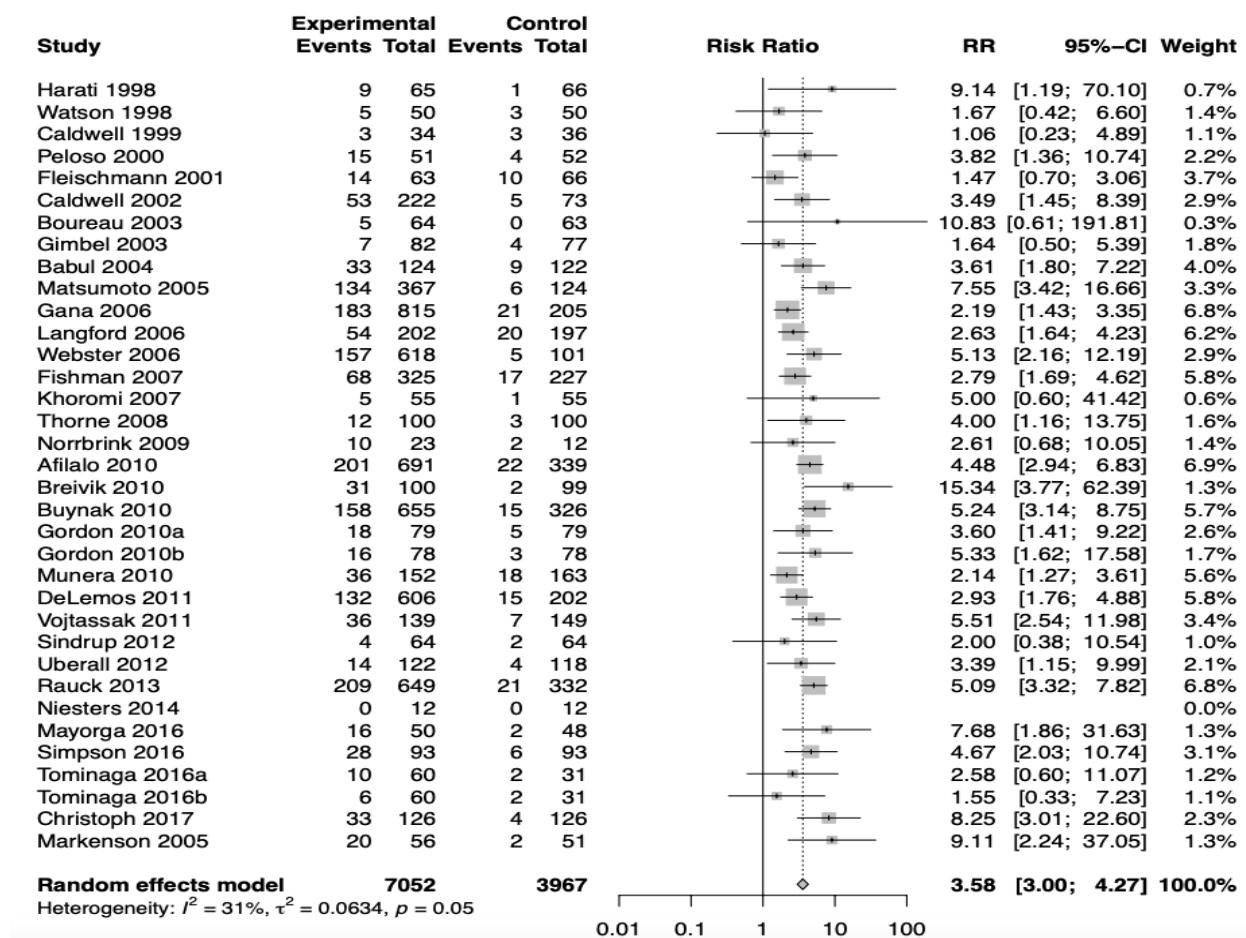
1
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5 eFigure 14. Discontinuations due to adverse events (enriched trials), opioids versus placebo pairwise meta-analysis random effect model
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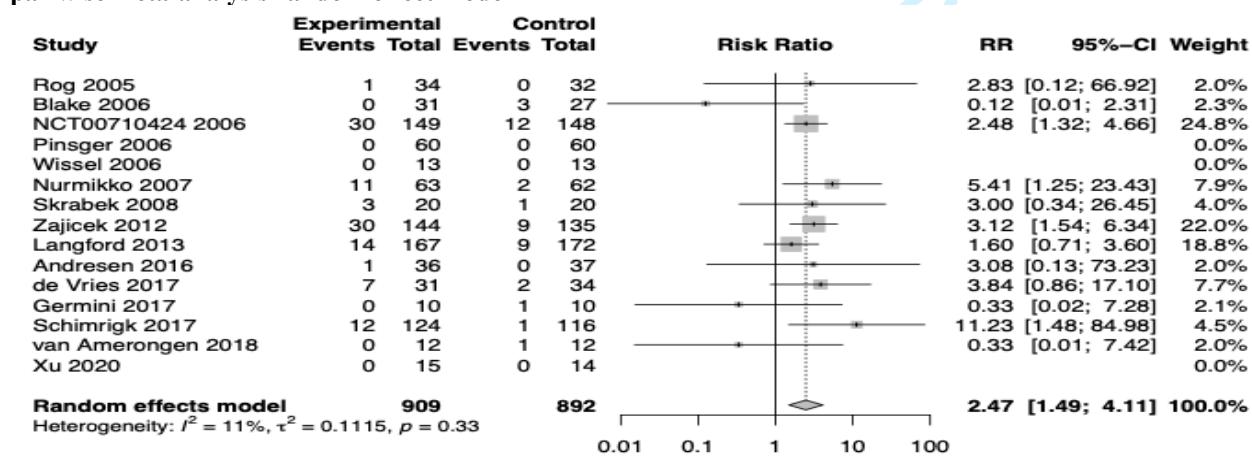
28 eFigure 15. Discontinuations due to adverse events (enriched trials), medical cannabis versus placebo
29 pairwise meta-analysis random effect model
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5 eFigure 16. Discontinuations due to adverse events (non-enriched trials), opioids versus placebo pairwise
6 meta-analysis random effect model
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40 eFigure 17. Discontinuations due to adverse events (non-enriched trials), medical cannabis versus placebo
41 pairwise meta-analysis random effect model
42



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5 **eAppendix 4: Reference list of medical cannabis studies with incomplete EQ-5D and SF-36 general health**
6 **data**

7 **EQ-5D:**

- 8 1. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel- group study
9 of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central
10 neuropathic pain in patients with multiple sclerosis. *J Neurol* 2013;260(4):984-97. doi: 10.1007/s00415-012-
11 6739-4 [published Online First: 2012/11/28]
12 2. Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel- group,
13 enriched-design study of nabiximols* (Sativex((R))), as add-on therapy, in subjects with refractory spasticity
14 caused by multiple sclerosis. *Eur J Neurol* 2011;18(9):1122-31. doi: 10.1111/j.1468-1331.2010.03328.x
15 [published Online First: 2011/03/03]
16 3. NCT00710424. A Study of Sativex® for Pain Relief Due to Diabetic Neuropathy:
17 <https://ClinicalTrials.gov/show/NCT00710424>, 2006.
18 4. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of
19 cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding
20 factor. *Diabetes Care* 2010;33(1):128-30. doi: 10.2337/dc09-1029 [published Online First: 2009/10/08]
21 5. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind,
22 placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic
23 peripheral neuropathic pain. *Pain* 2012;153(10):2073-82. doi: 10.1016/j.pain.2012.06.024 [published Online
24 First: 2012/08/28]

25 **SF-36 General health:**

- 26 1. Frank B, Serpell MG, Hughes J, et al. Comparison of analgesic effects and patient tolerability of nabilone and
27 dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ*
28 2008;336(7637):199-201. doi: 10.1136/bmj.39429.619653.80 [published Online First: 2008/01/10]
29 2. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel- group study
30 of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central
31 neuropathic pain in patients with multiple sclerosis. *J Neurol* 2013;260(4):984-97. doi: 10.1007/s00415-012-
32 6739-4 [published Online First: 2012/11/28]
33 3. Markova J, Essner U, Akmaz B, et al. Sativex((R)) as add-on therapy vs. further optimized first-line
34 ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled
35 randomised clinical trial. *Int J Neurosci* 2019;129(2):119-28. doi: 10.1080/00207454.2018.1481066 [published
36 Online First: 2018/05/25]
37 4. Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel- group,
38 enriched-design study of nabiximols* (Sativex((R))), as add-on therapy, in subjects with refractory spasticity
39 caused by multiple sclerosis. *Eur J Neurol* 2011;18(9):1122-31. doi: 10.1111/j.1468-1331.2010.03328.x
40 [published Online First: 2011/03/03]
41 5. NCT00710424. A Study of Sativex® for Pain Relief Due to Diabetic Neuropathy:
42 <https://ClinicalTrials.gov/show/NCT00710424>, 2006.
43 6. Schimrigk S, Marziniak M, Neubauer C, et al. Dronabinol Is a Safe Long-Term Treatment Option for
44 Neuropathic Pain Patients. *European neurology* 2017;78(5-6):320-29. doi: 10.1159/000481089 [published
45 Online First: 2017/10/27]
46 7. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of
47 cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding
48 factor. *Diabetes Care* 2010;33(1):128-30. doi: 10.2337/dc09-1029 [published Online First: 2009/10/08]

eTable 5. ICEMAN criteria for assessing the credibility of subgroup effects

Criteria	Subgroup effects of neuropathic vs non-neuropathic pain for outcomes below		
	Pain	Social function	Discontinuation due to adverse events (non-enriched)
1: Is the analysis of effect modification based on comparison within rather than between trials?	Between-study	Between-study	Between-study
2: For within-trial comparisons, is the effect modification similar from trial to trial?	Not applicable	Not applicable	Not applicable
3: For between-trial comparisons, is the number of trials large?	Large (55 studies with non-neuropathic pain; 26 studies with neuropathic pain)	Large (11 studies with non-neuropathic pain; 8 study with neuropathic pain)	Large (33 studies with non-neuropathic pain; 17 studies with neuropathic pain)
4: Was the direction of effect modification correctly hypothesized a priori?	Probably no (opposite)	Probably no (opposite)	Probably no (opposite)
5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification?	Chance an unlikely explanation ($p=0.004$)	Chance a likely explanation ($p=0.047$)	Chance a very likely explanation ($p=0.052$)
6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?	Probably no (5 factors)	Probably no (5 factors)	Probably no (5 factors)
7: Did the authors use a random effects model?	Definitely yes	Definitely yes	Definitely yes
8: If the effect modifier is a continuous variable, were arbitrary cut points avoided?	NA	NA	NA
9 Optional: Are there any additional considerations that may increase or decrease credibility?			
The effect modification persisted after adjustment for other potential effect modifiers	NA	NA	NA
The effect modification is consistent across related outcomes	Yes	Yes	Yes
A sensitivity analysis suggested robustness to relevant assumptions	NA	NA	NA
Effect modification supported by external evidence	NA	NA	NA
“Dose-response effect” across levels of the effect modifier	NA	NA	NA
Risk of bias of the main effects of the individual RCTs or the meta-analysis	NA	NA	NA
The meta-analysis had had exceptionally high power to detect the effect modification	NA	NA	NA
Overall credibility	Low	Very low	Very low

eTable 6. Subgroup analysis for secondary outcomes with low certainty evidence

Subgroup factors		Emotional functioning				Sleep quality				Discontinuations due to AEs (enriched studies)			
		No studies	WMD	95% CrI	p-value	No studies	WMD	95% CrI	p-value	No studies	OR	95% CrI	p-value
Clinical condition	Neuropathic	10	0.15	(-4.07, 4.56)	0.783	10	-3.44	(-12.56, 6.03)	0.323	4	NA	NA	NA
	Non-neuropathic	19	0.91	(-2.47, 4.08)		21	2.68	(-5.25, 10.38)		18	NA	NA	
Length of follow-up	≤ 2 months	13	0.80	(-4.77, 5.19)	0.965	16	-0.28	(-7.45, 7.26)	0.848	4			
	>2 months	17	0.93	(-2.11, 4.08)		16	0.75	(-6.96, 8.09)		18			
Adequate randomization	Yes	18	2.55	(-0.74, 5.64)	0.119	21	0.04	(-6.62, 6.70)	0.638	11	NA	NA	NA
	No	12	-1.14	(-4.54, 2.20)		11	3.21	(-8.92, 13.92)		11	2.05	(0.09, 93.28)	
Adequate concealment	Yes	22	1.44	(-0.91, 3.62)	NA	25	0.20	(-6.32, 6.44)	NA	15	0.91	(0.08, 10.88)	NA
	No	NA	NA	NA		NA	NA	NA		NA	NA	NA	
Industry funded trials	Yes	24	2.27	(-1.19, 5.68)	0.363	29	0.71	(-4.94, 6.20)	0.684	21	0.79	(0.07, 8.97)	NA
	No	5	-1.71	(-9.86, 5.86)		3	-3.12	(-20.25, 14.88)		NA	NA	NA	
Loss to follow-up	High (≥20%)	25	0.38	(-2.41, 3.04)	0.997	20	0.86	(-9.30, 10.66)	0.958	NA	NA	NA	NA
	Low (<20%)	5	0.36	(-8.02, 9.38)		12	1.13	(-11.54, 12.53)		5	0.65	(0.04, 10.18)	
Study design	Enrichment	7	4.05	(-10.97, 19.04)	0.695	6	7.27	(-4.35, 17.38)	0.184	-	-	-	-
	Non-enrichment	23	1.02	(-1.32, 3.12)		26	-1.21	(-7.49, 4.96)		-	-	-	

Results are medical cannabis versus opioids. Inadequate concealment not applicable because all medical cannabis trials had adequate concealment.

p-value based on test of interaction

eTable 7. Network meta-regression for pain outcome, length of follow-up and sample size

Pain relief, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Medical cannabis
		Unadjusted model	
Placebo	Adjusted model		-0.60 (-0.87, -0.33)
Medical cannabis		-1.39 ¹ (-2.04, -0.76)	
Opioids		-1.21 ² (-1.53, -0.91)	0.18 ³ (-0.55, 0.89)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		-0.60 (-0.87, -0.33)
Medical cannabis		-0.91 ¹ (-1.37, -0.46)	
Opioids		-0.97 ² (-1.15, -0.78)	-0.06 ³ (-0.54, 0.44)

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for medical cannabis versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus medical cannabis. DIC value between adjusted and unadjusted models is less than 5

eTable 8. Network meta-regression for secondary outcomes, length of follow-up and sample size

Physical functioning, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Medical cannabis
		Unadjusted model	
Placebo	Adjusted model		2.52 (0.37, 4.91)
Medical cannabis		7.23 ¹ (2.10, 12.77)	
Opioids		3.00 ² (0.43, 5.84)	-4.20 ³ (-10.32, 1.54)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		2.52 (0.37, 4.91)
Medical cannabis		4.19 ¹ (0.94, 7.57)	
Opioids		2.75 ² (1.16, 4.65)	-1.44 (-5.08, 2.33)

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for medical cannabis versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus medical cannabis. DIC value between adjusted and unadjusted models is less than 5

Emotional functioning, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Medical cannabis
		Unadjusted model	
Placebo	Adjusted model		0.70 (-1.42, 2.84)
Medical cannabis		0.96 ¹ (-4.81, 6.57)	
Opioids		0.32 ² (-2.68, 3.59)	-0.67 ³ (-6.78, 5.92)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		0.70 (-1.42, 2.84)
Medical cannabis		1.11 ¹ (-2.04, 4.24)	
Opioids		0.59 ² (-0.99, 2.31)	-0.50 ³ (-3.98, 3.06)

¹ MD for medical cannabis versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus medical cannabis. DIC value between adjusted and unadjusted models is less than 5

Role functioning, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Medical cannabis
		Unadjusted model	
Placebo	Adjusted model		0.88 (-3.78, 6.05)
Medical cannabis		14.41 ¹ (-0.89, 31.01)	
Opioids		2.22 ² (-2.95, 8.49)	-12.11 ³ (-29.35, 4.07)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		0.88 (-3.78, 6.05)
Medical cannabis		5.40 ¹ (-5.80, 16.94)	
Opioids		2.25 ² (-0.87, 5.72)	-3.13 ³ (-14.98, 8.65)

¹ MD for medical cannabis versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus medical cannabis. DIC value between adjusted and unadjusted models is less than 5

Social functioning, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Medical cannabis
		Unadjusted model	
Placebo	Adjusted model		1.70 (-3.28, 8.13)
Medical cannabis		2.43 ¹ (-7.21, 12.74)	
Opioids		1.98 ² (-3.14, 6.89)	-0.37 ³ (-11.76, 10.10)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		1.70 (-3.28, 8.13)
Medical cannabis		0.16 ¹ (-7.66, 8.04)	
Opioids		1.61 ² (-1.10, 4.27)	1.45 ³ (-6.89, 9.64)

¹ MD for medical cannabis versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus medical cannabis. DIC value between adjusted and unadjusted models is less than 5

Sleep quality, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Medical cannabis
Unadjusted model			
Placebo	Adjusted model		5.95 (1.82, 10.24)
		8.74 ¹ (−1.97, 19.32)	
		9.10² (1.91, 16.26)	0.28 ³ (−12.32, 13.04)
Covariate, sample size			
Placebo	Adjusted model		Unadjusted model
			5.95 (1.82, 10.24)
		7.40 ¹ (0.75, 14.02)	
Opioids	Adjusted model	8.56 ² (4.41, 12.75)	1.16 ³ (−6.58, 9.00)

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for medical cannabis versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus medical cannabis. DIC value between adjusted and unadjusted models is less than 5

Discontinuations due to adverse events (enriched trials)			
Results are not reliable due to small number of studies. Number of studies for medical cannabis versus placebo = 2.			

Discontinuations due to adverse events (non-enriched trials), network estimate OR (95% CrI)			
Covariate, length of follow-up		Placebo	Medical cannabis
Unadjusted model			
Placebo	Adjusted model		1.80 (1.19, 2.63)
		0.75 ¹ (0.27, 1.84)	
		2.05² (1.40, 2.95)	2.70 ³ (1.08, 8.13)
Covariate, sample size			
Placebo	Adjusted model		Unadjusted model
			1.80 (1.19, 2.63)
		0.79 ¹ (0.32, 1.83)	
Opioids	Adjusted model	2.87 ² (2.15, 3.79)	3.65 ³ (1.54, 9.22)

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for medical cannabis versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus medical cannabis.

eTable 9. Network meta-analysis results for pain outcome by MME thresholds

Placebo	Medical cannabis	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
-0.61 (-0.90, -0.32)				
-0.92 (-1.23, -0.62)	-0.31 (-0.73, 0.11)			
-0.81 (-1.04, -0.58)	-0.20 (-0.56, 0.17)	0.11 (-0.27, 0.49)		
-0.81 (-1.06, -0.55)	-0.20 (-0.58, 0.19)	0.11 (-0.28, 0.51)	0.00 (-0.34, 0.34)	

All values in bold are statistically significant at the 0.05 significance level

eTable 10. Network meta-analysis results for secondary outcomes by MME thresholds

Physical functioning

Placebo	Medical cannabis	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
2.30 (0.35, 4.66)				
1.14 (-1.28, 3.63)	-1.14 (-4.61, 1.88)			
2.25 (0.75, 4.26)	-0.04 (-2.65, 2.59)	1.10 (-1.66, 4.36)		
3.17 (1.47, 5.23)	0.88 (-1.96, 3.56)	2.02 (-0.91, 5.28)	0.93 (-1.64, 3.29)	

All values in bold are statistically significant at the 0.05 significance level

Emotional functioning

Placebo	Medical cannabis	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
0.66 (-1.01, 2.36)				
-1.11 (-2.40, 0.34)	-1.76 (-3.89, 0.44)			
0.07 (-1.28, 1.42)	-0.59 (-2.75, 1.52)	1.17 (-0.83, 3.03)		
-1.29 (-2.35, 0.37)	-1.93 (-3.87, 0.40)	-0.19 (-1.83, 1.96)	-1.36 (-2.96, 0.87)	

Role functioning

Placebo	Medical cannabis	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
1.08 (-4.16, 6.90)				
-2.70 (-8.69, 3.17)	-3.77 (-12.25, 3.97)			
2.77 (-1.51, 8.36)	1.72 (-5.28, 9.30)	5.47 (-1.54, 13.89)		
0.48 (-4.29, 5.37)	-0.61 (-8.18, 6.47)	3.19 (-4.34, 10.91)	-2.28 (-9.85, 3.98)	

Social functioning

Placebo	Medical cannabis	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
-1.33 (-5.06, 1.68)	-0.58 (-5.42, 4.77)			
-1.91 (-5.87, 1.82)				
-0.35 (-4.96, 4.41)	1.00 (-4.44, 7.11)	1.57 (-4.33, 7.76)		
1.93 (-1.13, 5.82)	3.26 (-0.97, 8.96)	3.84 (-0.81, 9.61)	2.30 (-3.22, 8.34)	

Sleep quality

Placebo	Medical cannabis	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
5.93 (1.82, 10.24)	-5.86 (-18.31, 6.37)			
0.09 (-11.56, 11.64)				
4.39 (-0.12, 9.36)	-1.54 (-7.72, 4.88)	4.29 (-7.92, 17.09)		
9.56 (4.73, 14.56)	3.62 (-2.87, 10.08)	9.47 (-3.02, 22.16)	5.17 (-1.77, 11.81)	

All values in bold are statistically significant at the 0.05 significance level

Discontinuations due to adverse events (enriched trials)

Placebo	Medical cannabis	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
0.99 (0.10, 10.65)				
1.23 (0.71, 2.18)	1.25 (0.11, 13.76)			
1.07 (0.63, 1.80)	1.07 (0.10, 11.38)	0.87 (0.40, 1.84)		
1.52 (0.80, 2.72)	1.52 (0.13, 16.32)	1.23 (0.53, 2.73)	1.42 (0.63, 3.12)	

Discontinuations due to adverse events (non-enriched trials)

Placebo	Medical cannabis	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
1.83 (1.19, 2.67)				
3.45 (2.12, 5.28)	1.88 (1.06, 3.44)			
2.92 (2.28, 3.88)	1.60 (1.01, 2.74)	0.85 (0.52, 1.51)		
4.02 (2.86, 5.31)	2.19 (1.36, 3.57)	1.17 (0.68, 1.98)	1.38 (0.86, 1.99)	

All values in bold are statistically significant at the 0.05 significance level

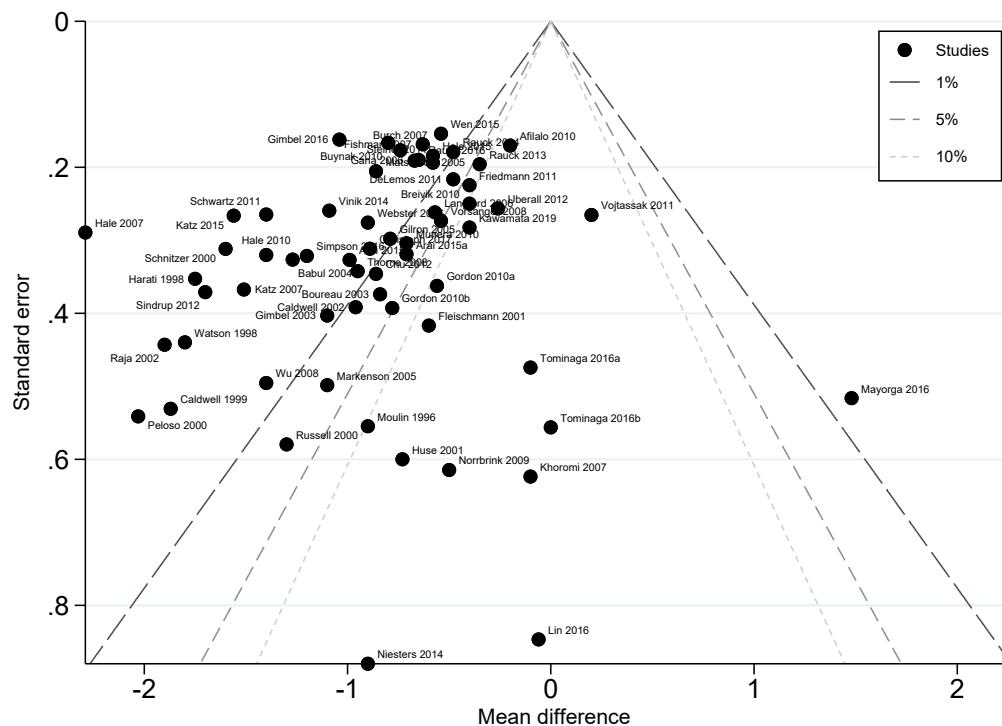
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5 **eTable 11. Pain studies from JAMA 2018 systematic review & meta-analysis included & excluded in network
6 meta-analysis**

Author	Year	Inclusion or Exclusion reason	Author	Year	Inclusion or Exclusion reason
Fleischmann	2001	Included	Schwartz	2011	Included
Bennett	2003	Combination products	Steiner	2011	Included
Ruoff	2003	Combination products	Vojtassak	2011	Included
Babul	2004	Included	Rauck	2013	Included
Emkey	2004	Combination products	Rauck	2014	Included
Peloso	2004	Combination products	Vinik	2014	Included
Gana	2006	Included	Arai	2015	Included
Webster	2006	Included	Arai	2015	Included
Burch	2007	Included	Hale	2015	Included
Fishman	2007	Included	Katz	2015	Included
Hale	2007	Included	Rauck	2015	Combination products
Katz	2007	Included	Trenkwalder	2015	Combination products
Hanna	2008	Combination products	Wen	2015	Included
Vorsanger	2008	Included	Gimbel	2016	Included
Afilalo	2010	Included	Mayorga	2016	Included
Breivik	2010	Included	Rauck	2016	Included
Buynak	2010	Included	Simpson	2016	Included
Hale	2010	Included	Tominaga	2016	Included
Katz	2010	Combination products	Tominaga	2016	Included
DeLemos	2011	Included	Christoph	2017	Included
Friedmann	2011	Included	Serrie	2017	Incomplete reporting
Total number of studies 42; 9 exclusions; 33 inclusions					

32
33
34 **eTable 12. Pain studies included in network meta-analysis excluded from pain JAMA 2018 systematic review
35 & meta-analysis**

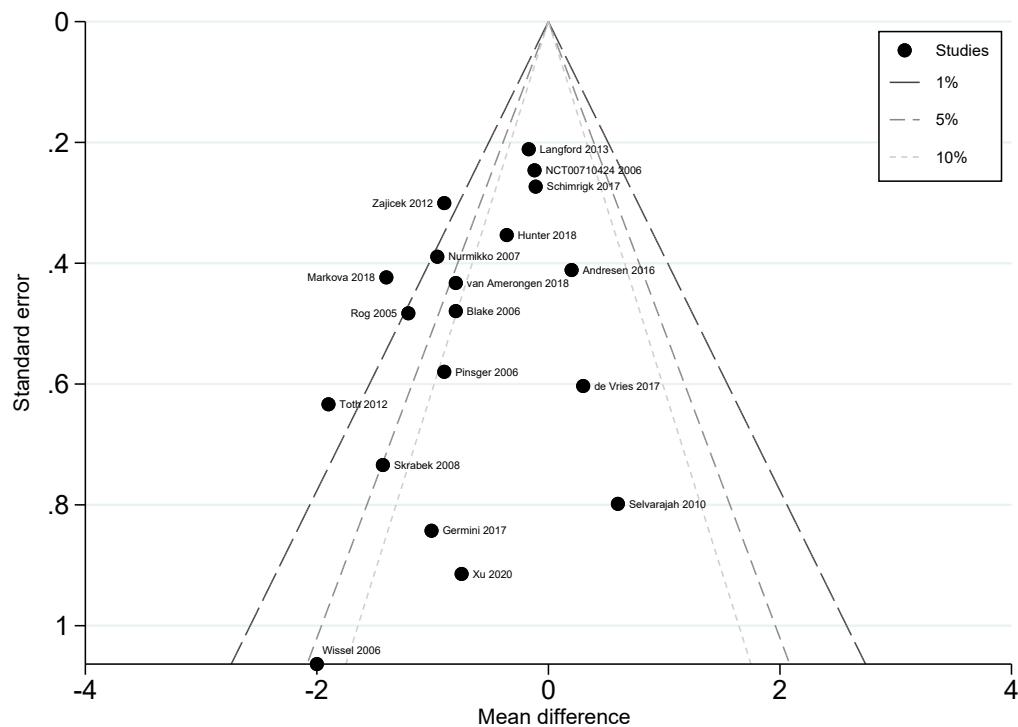
Author	Year	Exclusion reason from JAMA review	Author	Year	Exclusion reason from JAMA review
Moulin	1996	< 3months follow-up	Langford	2006	< 3months follow-up
Harati	1998	< 3months follow-up	Khoromi	2007	< 3months follow-up
Watson	1998	< 3months follow-up	Thorne	2008	< 3months follow-up
Caldwell	1999	< 3months follow-up	Wu	2008	Did not pass screening
Peloso	2000	< 3months follow-up	Norrbrink	2009	< 3months follow-up
Russell	2000	< 3months follow-up	Gordon	2010	< 3months follow-up
Schnitzer	2000	< 3months follow-up	Gordon	2010	< 3months follow-up
Huse	2001	< 3months follow-up	Munera	2010	< 3months follow-up
Caldwell	2002	< 3months follow-up	Chu	2012	< 3months follow-up
Raja	2002	< 3months follow-up	Sindrup	2012	< 3months follow-up
Boureau	2003	< 3months follow-up	Uberall	2012	< 3months follow-up
Gimbel	2003	< 3months follow-up	Niesters	2014	< 3months follow-up
Gilron	2005	< 3months follow-up	Lin	2016	< 3months follow-up
Markenson	2005	Did not pass screening	Kawamata	2019	Published after search execution end date
Matsumoto	2005	< 3months follow-up			
Total number of studies 29.					

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3 **eFigure 18. Funnel plot for pain for randomized trials of opioids versus placebo**

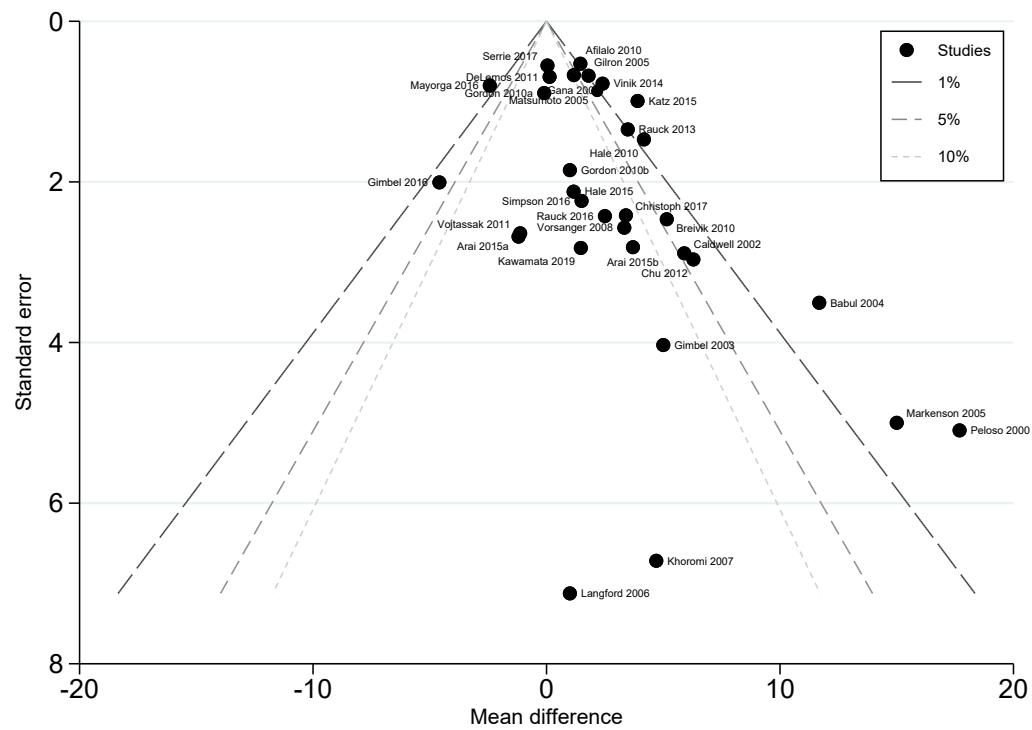


Egger's test p-value = 0.039

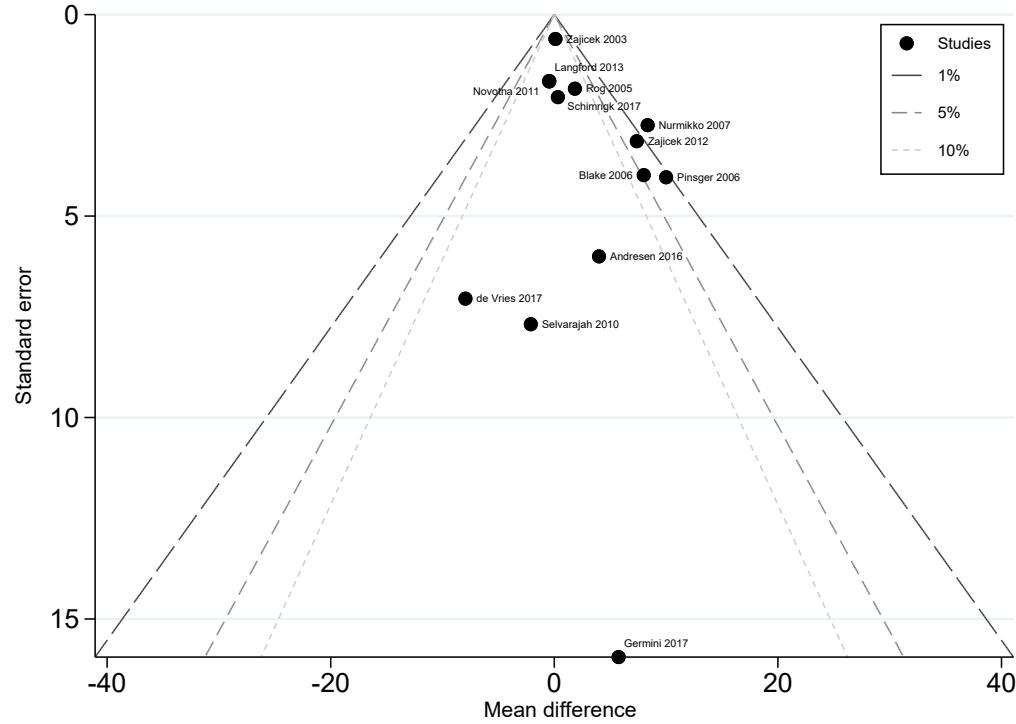
30 **eFigure 19. Funnel plot for pain for randomized trials of medical cannabis versus placebo**



Egger's test p-value = 0.044

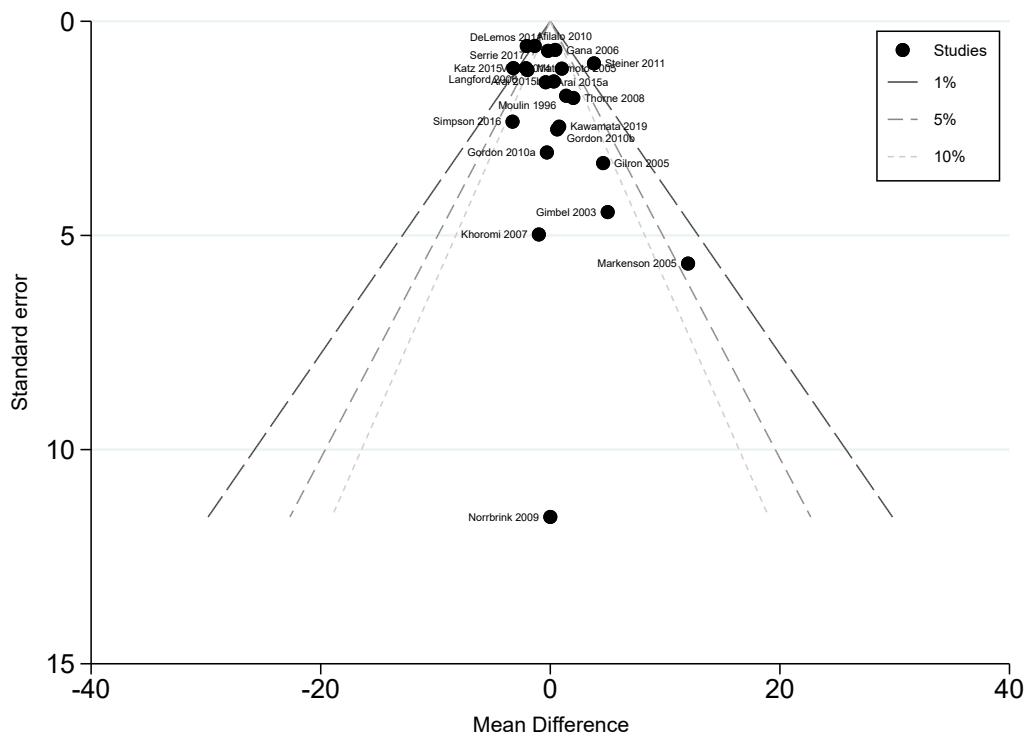
eFigure 20. Funnel plot for physical functioning for randomized trials of opioids versus placebo

Egger's test p-value = 0.015

eFigure 21. Funnel plot for physical functioning for randomized trials of medical cannabis versus placebo

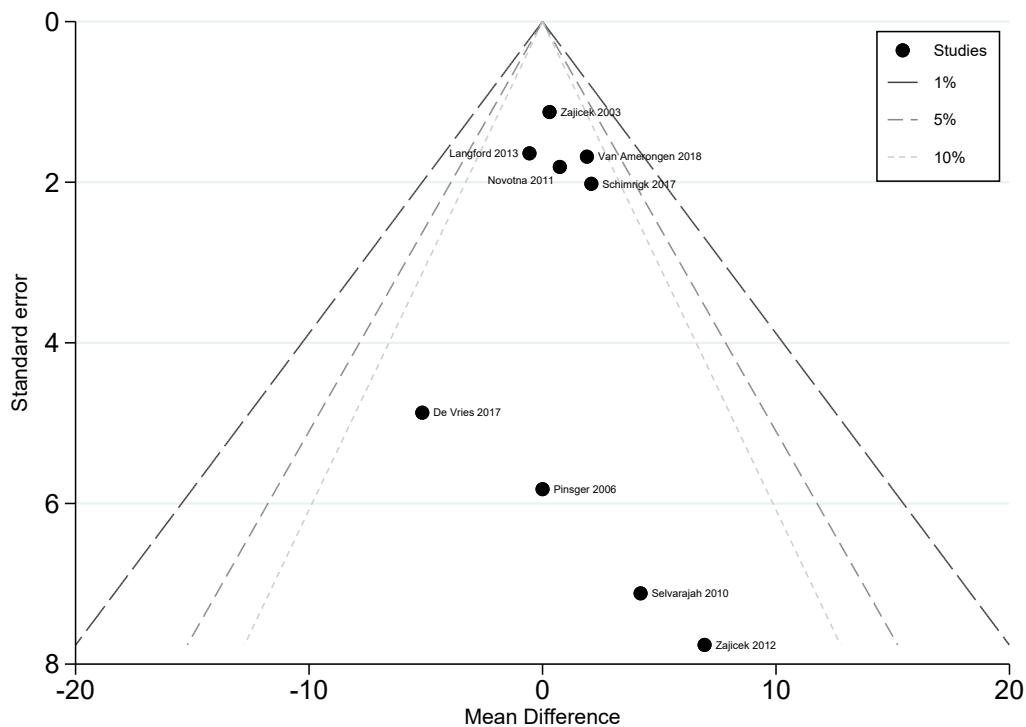
Egger's test p-value = 0.098

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3 **eFigure 22. Funnel plot for emotional functioning for randomized trials of opioids versus placebo**
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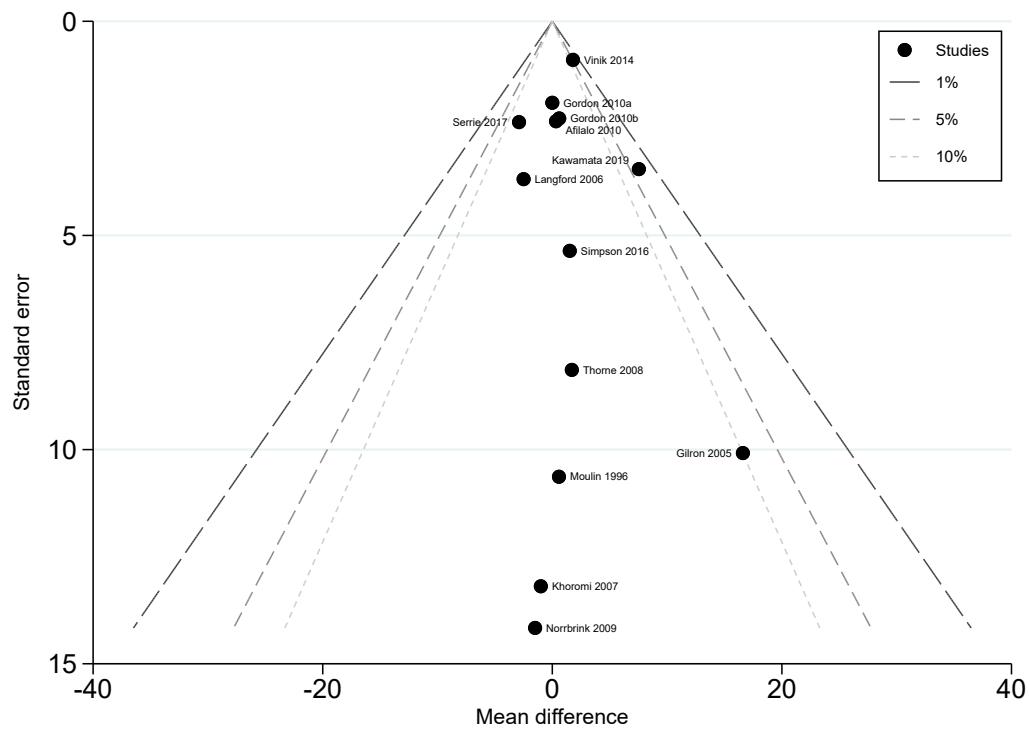
Egger's test p-value = 0.121

30 **eFigure 23. Funnel plot for emotional functioning for randomized trials of medical cannabis versus placebo**



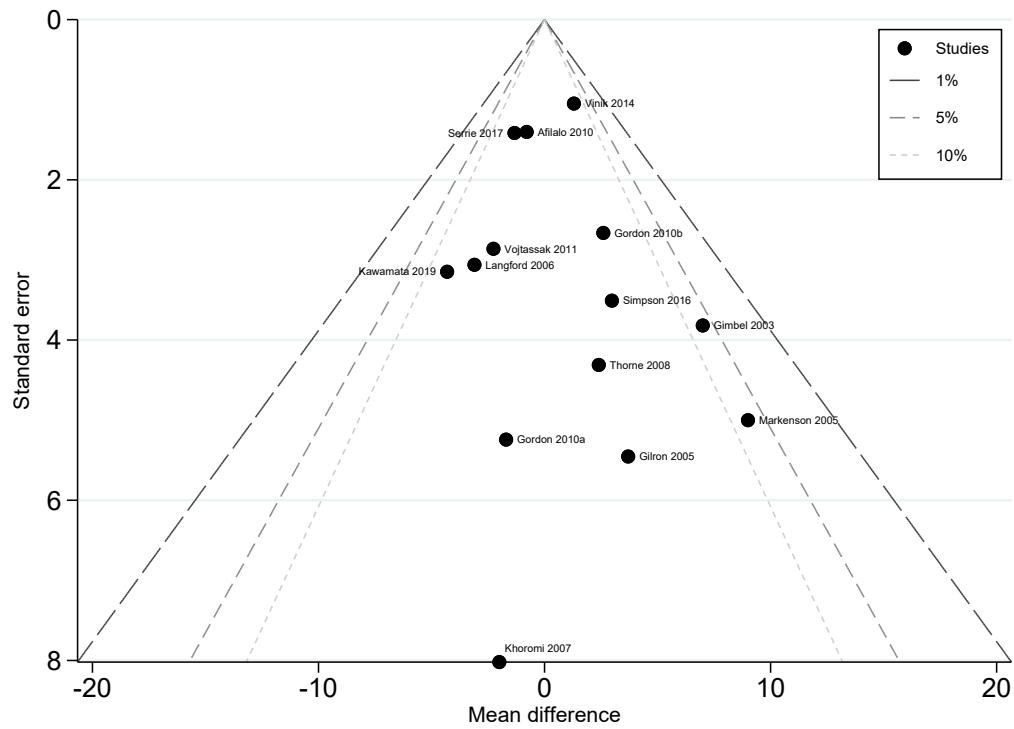
Egger's test p-value = 0.71

eFigure 24. Funnel plot for role functioning for randomized trials of opioids versus placebo



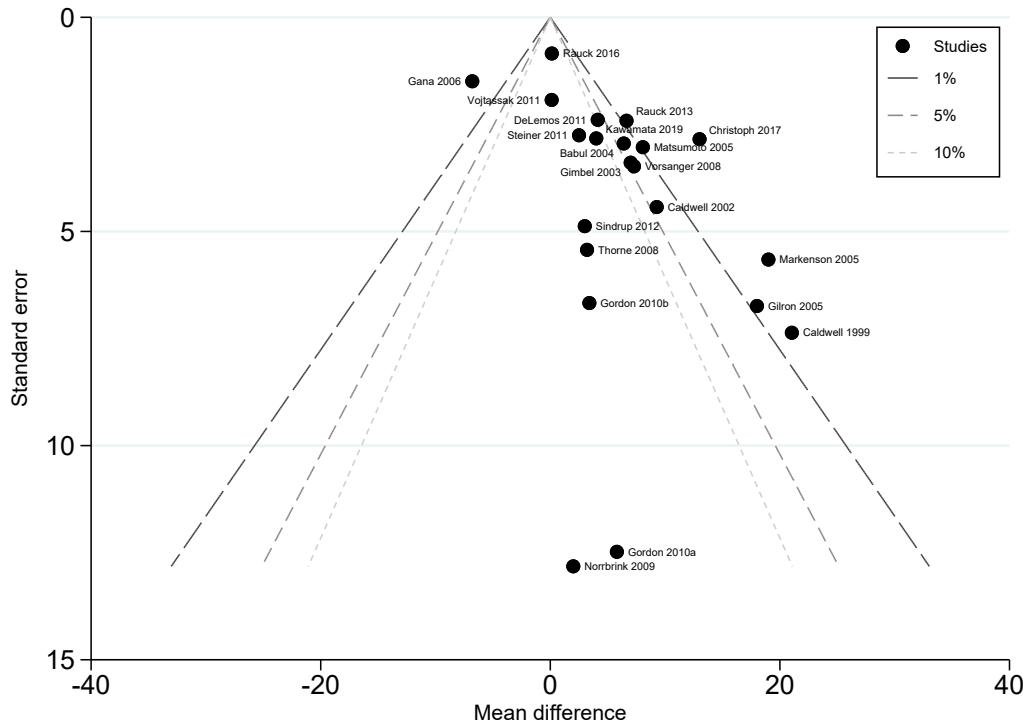
Egger's test p-value = 0.967

eFigure 25. Funnel plot for social functioning for randomized trials of opioids versus placebo



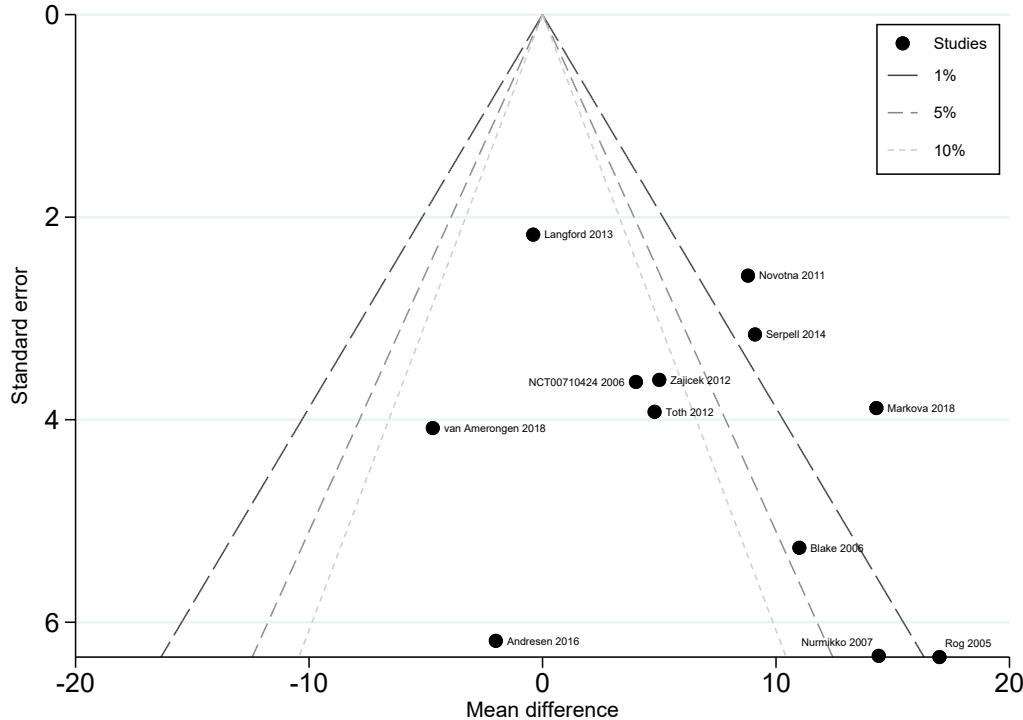
Egger's test p-value = 0.548

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28 Egger's test p-value = 0.003
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31 **eFigure 27. Funnel plot for sleep quality for randomized trials of medical cannabis versus placebo**
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55 Egger's test p-value = 0.258
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Cannabis for medical use versus opioids for chronic noncancer pain: A systematic review and network meta-analysis of randomized clinical trials

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Cannabis for medical use versus opioids for chronic noncancer pain: A systematic review and network meta-analysis of randomized clinical trials

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ABSTRACT**OBJECTIVE**

To evaluate the comparative benefits and harms of opioids and cannabis for medical use for chronic noncancer pain.

DESIGN

Systematic review and network meta-analysis.

DATA SOURCES

EMBASE, MEDLINE, CINAHL, AMED, PsycINFO, PubMed, Web of Science, Cannabis-Med, Epistemonikos and the Cochrane Library (CENTRAL) from inception to March 2021.

STUDY SELECTION

Randomized trials comparing any type of cannabis for medical use or opioids, against each other or placebo, with patient follow-up ≥ 4 weeks.

DATA EXTRACTION AND SYNTHESIS

Paired reviewers independently extracted data. We used Bayesian random-effects network meta-analyses to summarize the evidence and the GRADE approach to evaluate the certainty of evidence and communicate our findings.

RESULTS

Ninety trials involving 22 028 patients were eligible for review, among which the length of follow-up ranged from 28 to 180 days. Moderate certainty evidence showed that opioids provide small improvements in pain, physical functioning, and sleep quality vs. placebo; low to moderate certainty evidence supported similar effects for cannabis vs. placebo. Neither were more effective than placebo for role, social or emotional functioning (all high to moderate certainty evidence). Moderate certainty evidence showed there is probably little to no difference between

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3 cannabis for medical use and opioids for physical functioning (weighted mean difference
4 [WMD] 0.47 on the 100-point SF-36 physical component summary score, 95% CrI -1.97 to
5 2.99), and cannabis resulted in fewer discontinuations due to adverse events vs. opioids (odds
6 ratio 0.55, 95% CrI 0.36 to 0.83). Low certainty evidence suggested little to no difference
7 between cannabis and opioids for pain relief (WMD 0.23cm on a 10cm visual analogue scale
8 [VAS], 95% CrI -0.06 to 0.53) or sleep quality (WMD 0.49mm on a 100mm VAS, 95% CrI -
9 4.72 to 5.59).

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19 **CONCLUSIONS**
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22 Cannabis for medical use may be similarly effective and result in fewer discontinuations than
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24 opioids for chronic noncancer pain.
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PROSPERO registration number

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Word count: 298

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6 Strengths and limitations of this study
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- 8
- 9 • This is the first network meta-analysis exploring the comparative effectiveness of
 - 10 cannabis for medical use and opioids for management of chronic noncancer pain.
 - 11
 - 12 • We conducted a comprehensive search for eligible trials and used the GRADE approach
 - 13 to appraise the certainty of evidence for treatment effects and focused our analysis on
 - 14 patient-important outcomes.
 - 15
 - 16 • Twenty-four RCTs evaluating cannabis for medical use were included in our review;
 - 17 however, none of these trials administered inhaled forms of cannabis and the
 - 18 generalizability of our findings to smoked or vaporized cannabis is uncertain.
 - 19
 - 20 • For the comparison of cannabis for medical use and opioids, the majority of our
 - 21 outcomes were informed by indirect evidence since we found only one trial directly
 - 22 comparing both interventions for chronic pain.
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Introduction

Chronic noncancer pain impacts 20% of the global population and is associated with reduced quality of life, disability, and considerable socioeconomic burden [1-4]. Opioids are commonly prescribed for chronic noncancer pain and may provide improvement in pain relief, physical functioning and quality of sleep compared to placebo [5]; however, they are also associated with harms including addiction, overdose and death [6,7]. There is growing interest in cannabis as an alternative to long-term opioid use [8], and countries increasingly permit therapeutic use of cannabis [9]. Two-thirds of cannabis for medical use users endorse management of chronic pain as their indication for use [10]. Despite increasing availability of cannabis for medical use its' use for chronic pain remains controversial due, in part, to conflicting recommendations. A 2019 guideline from the National Institute for Health and Care Excellence (NICE) made strong recommendations against use of cannabis for chronic pain, and in 2021 the International Association for the Study of Pain (IASP) released a position statement against the use of cannabinoids for pain [11,12]. Alternately, a 2021 BMJ Rapid Recommendation made a conditional recommendation to offer a trial of non-inhaled cannabis for medical use for people living with chronic pain if standard care was insufficient [13]. The European Pain Federation (EFIC) also issued a position paper stating that cannabis based medicines can be used by experienced physicians when guideline recommended 1st and 2nd line therapies for chronic pain do not provide sufficient benefit [14]. We undertook a systematic review and network meta-analysis of randomized controlled trials (RCTs) to explore the comparative benefits and harms of cannabis for medical use and opioids for chronic noncancer pain.

Methods

We adhered to the Preferred Reporting items for Systematic reviews and Meta-Analyses extension statement for network meta-analysis (PRISMA-NMA) [15], registered our review on PROSPERO (CRD42020185184) [16], and followed GRADE guidance for communicating our findings [17].

Data Sources and Searches

We searched EMBASE, MEDLINE, CINAHL, AMED, PsycINFO, PubMed, Web of Science, Cannabis-Med, Epistemonikos and the Cochrane Library (CENTRAL) from inception to March 2021, without language restrictions. An experienced medical librarian developed database-specific search strategies (eAppendix 1 in Supplement). We reviewed reference lists of eligible studies, and relevant reviews and guidelines, to identify additional studies. We included RCTs that enrolled ≥ 20 patients with chronic noncancer pain (pain lasting ≥ 3 months), randomized them to any type of cannabis for therapeutic use, an opioid, or placebo and followed them for ≥ 4 weeks to allow for sufficient time for functional outcomes to manifest among treatment responders [13]. Trials including patients with chronic cancer and noncancer pain were included if outcome data were reported separately. We excluded conference abstracts and trials of combination products (e.g., opioids with nonsteroidal anti-inflammatory drugs or anti-depressants).

Pairs of reviewers independently screened titles and abstracts, and full text reports, and extracted data using standardized, pilot-tested forms using online systematic review software (DistillerSR, Evidence Partners, Ottawa, Canada; <http://systematic-review.net/>). For all eligible trials, we (W.L., N.A. C.R, J.H.M) collected information regarding study characteristics, intervention

details, patient characteristics, and all patient-important outcomes as guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials [18,19]. Discrepancies were resolved by discussion or, when necessary, by an adjudicator.

Risk of Bias Assessment

Risk of bias was assessed for eligible studies, independently and in duplicate, by pairs of reviewers using a modified Cochrane risk of bias instrument (RoB 1.0) according to the following domains: random sequence generation, allocation concealment, blinding of participants, caregivers, outcome assessors, and data analysts, and loss to follow-up ($\geq 20\%$ missing data was considered high risk of bias) [20,21].

Data Analysis

Instruments used in the RCTs mostly consisted of the visual analogue scale (VAS) and the numerical rating scale (NRS) for measuring pain intensity and sleep quality, and the Short Form-36 for other important patient outcomes (e.g. physical functioning, emotional functioning, role functioning, social functioning). These instruments have been shown to be reliable and valid in chronic pain populations [22-24]. eTable 1 lists additional instruments that were used to capture patient-important outcomes, and references supporting their psychometric properties. We converted continuous measures to common scales on a domain-by-domain basis when different instruments were used to measure the same construct by re-scaling the mean and SD of the other instruments: (1) pain relief to a 10cm visual analogue scale (VAS); (2) physical functioning to the 100-point 36-item Short Form Survey (SF-36) physical component summary (PCS) score; (3) emotional functioning to the 100-point SF-36 mental component summary (MCS) score; (4) role

functioning to the 100-point SF-36 subscale for role limitations due to physical problems; (5) social functioning to the 100-point SF-36 subscale for social functioning; and (6) sleep quality to a 100-mm VAS [25].

We calculated direct estimates for any comparison reported by two or more studies as the weighted mean difference (WMD) and associated 95% credible interval (95% CrI) using change score from baseline to the end of follow-up to address interpatient variability. When standard deviations (SDs) for continuous outcomes were not reported by study authors, they were estimated using confidence intervals or exact p-values [26]. To optimize interpretability of our findings for statistically significant continuous outcomes, we used the network estimate of treatment effects to model the risk difference (RD) for achieving the minimally important difference (MID) or higher. We used an MID of 1cm for the 10-cm VAS for pain [27], 10mm for sleep quality, 10-points for SF-36 subscales (role and social functioning), and 5-points for SF-36 PCS and MCS scores [28,29].

For discontinuations due to adverse events, we used a binomial likelihood distribution and logit link to generate the pooled odds ratio (OR) with corresponding 95% CrI. We constructed separate models for enriched and non-enriched trials, as enriched trials typically exclude patients who report problematic adverse events during an open-label run-in period prior to randomization [30]. For estimating the number of patients expected to discontinue due to adverse events, we calculated the absolute effects for network estimates by multiplying the OR and its 95% CrI with the estimated baseline risk for discontinuations due to adverse events. We used median risk in the placebo group of included randomized trials as the baseline risk.

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5 For studies that reported outcomes at several timepoints, we used data from the longest follow-
6 up. We performed all conventional pairwise meta-analyses using DerSimonian and Laird
7 random-effects models. Heterogeneity between RCTs for each direct comparison was assessed
8 with visual inspection of forest plots and the I^2 statistic [31]. For all direct comparisons, we
9 assessed small study effects using funnel plots and Egger's test when 10 or more trials were
10 available [32].
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22 The feasibility of conducting a random effects Bayesian NMA was assessed for all outcomes –
23 this included assessing homogeneity of included studies, patients, and intervention
24 characteristics, and network connectivity. We used edge-splitting (side-splitting) to evaluate the
25 consistency of relative treatment effects between direct (e.g. pairwise meta-analysis) and indirect
26 evidence, and leverage plots to visually inspect model fit [33]. Models were programmed with
27 three chains, and the convergence assessed using the Gelman-Rubin statistic [34]. All analyses
28 began with a burn-in phase (1000 iterations) followed by 100 000 iterations with 1000
29 adaptations. We used non-informative priors with mean 0 and standard deviation $15u$, where u is
30 the largest maximum likelihood estimator of treatment differences on the linear scale in single
31 trials [35]. Statistical superiority was asserted when the 95% CrI excluded the null effect (i.e., 0.0
32 for WMDs and 1.0 for ORs). All analyses were programmed in R v3.5.3 ([https://www.R-](https://www.R-project.org)
33 project.org) using BUGSnet [35].
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We tested the following a priori subgroup hypotheses that treatment effects were associated with:
(1) neuropathic vs. non-neuropathic pain; (2) shorter vs. longer (≤ 2 months vs > 2 months)

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3 follow-up; (3) trials at risk of bias (on a criterion-by-criterion basis); (4) enriched enrollment
4 trials vs not enriched; and (5) higher opioid doses versus lower opioid doses by evaluating the
5 following morphine milligram equivalent (MME) per day thresholds: (i) high = MME > 100 mg;
6 (ii) intermediate = MME 50 – 99 mg; and (iii) low = MME < 50 mg. We assessed the credibility
7 of significant subgroup effects (i.e., test of interaction $p \leq 0.05$) with the ICEMAN tool [36]. We
8 used network meta-regression to explore the association between treatment effects and length of
9 follow-up and sample size. The deviance information criterion (DIC) was used to assess model
10 fit.
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24 **Quality of Evidence**

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26 We used the Grading of Recommendations, Assessment, Development and Evaluations
27 (GRADE) approach to assess certainty of the evidence for all outcomes and effect estimates from
28 network meta-analysis [37]. Ratings of the certainty of evidence for direct and indirect estimates
29 included assessment of risk of bias, inconsistency, indirectness, publication bias, and
30 intransitivity (only for indirect estimates). We judged network estimates as imprecise if the 95%
31 CrI included half the MID for continuous outcomes (e.g., 0.5 cm for pain) or the null effect (OR
32 of 1) for discontinuation due to adverse events.
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43 **Role of the funding source**

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45 The funders had no role in study design, data collection, analysis, interpretation or writing of the
46 manuscript, or the decision to submit.
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52 **Patient and Public Involvement**

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54 Patients and public were not involved in this research.
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Results

Of 20 012 citations identified, 90 studies from 89 publications proved eligible for review (Figure 1, eAppendix 2-3 in Supplement). No trials of inhaled cannabis were eligible for our review due to inadequate duration of follow-up (<4 weeks). Sixty-six trials compared opioids to placebo [38-102], 23 trials compared cannabis for medical use to placebo [103-125], and 1 trial [126] randomized patients to nabilone or dihydrocodeine. The evidence network for all our outcomes are presented in Figure 2. Among the included studies, the median of the mean age of participants was 56 years (interquartile range [IQR] 50 to 62), 58% were female, the median of the mean duration of pain was 8.1 years (IQR 5.0 to 12.7), and the median of the mean pain score at enrollment was 6.05 (IQR 4.65 to 6.90). Twenty-nine trials enrolled patients with neuropathic pain, 60 with non-neuropathic pain, and 1 trial enrolled patients with mixed pain. (Table 1, & eTable 2 in Supplement for details on the pain conditions and other baseline characteristics).

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Table 1: Summary of study participant characteristics included in eligible randomized
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control trials

No of trials	No of patients	Age, median of mean (IQR)	% female, median of mean (IQR)	Baseline pain score, median of mean (min – max)	No of studies by pain type*	No of studies by Intervention dose/format*	Follow-up, median days (min – max)	Trial type*
Opioids versus placebo								
66	18,401	58 (50 to 62)	56 (44.5 to 62)	6.01 (1.87-7.83)	Neuropathic pain, n = 18 (27%) Non-neuropathic, n = 47 (71%) Mixed, n = 1 (2%)	MME > 90mg, n = 14 (21%) MME 50 – 90mg, n = 19 (29%) MME < 50 mg, n = 21 (32%) Dose details Not reported n = 12 (18%)	84 (28–180)	Enriched n = 20 (30%) Non-enriched n = 46 (70%)
Cannabis for medical use versus placebo								
23	3,435	53 (50 to 58)	62 (40 to 70)	6.28 (2.15–7.80)	Neuropathic pain, n = 10 (43%) Non-neuropathic, n = 13 (57%)	PEA, n = 2 (9%) THC/CBD, n = 11 (48%) THC, n = 7 (30%) CBD n = 2 (9%) CBDV n = 1 (4%)	51 (28–112)	Enriched n = 3 (13%) Non-enriched n = 20 (87%)
Cannabis for medical use versus opioids								
1	192	50	26	6.72	Neuropathic pain, n = 1 (100%)	THC, n = 1 (100%)	42	Non-enriched n = (100%)

31 * Values in parenthesis are percentage of trials

32 **IQR, interquartile range.

33 CBDV, Cannabidiolvarin

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5 Most trials (75 of 90; 83%) were judged to be at high risk of bias for at least one domain.
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7 Adequate generation of a randomization sequence was reported by 53 (59%) trials, 64 (71%)
8 reported concealment of allocation, and almost all trials reported blinding of patients (99%) and
9 healthcare providers and data collectors (98%). (eTable 3 in Supplement). Sixty-five (72%) trials
10 reported $\geq 20\%$ missing outcome data. (eTable 3 in Supplement). We did not find evidence of
11 incoherence. For closed loop networks, consistency was met based on DIC values. For open loop
12 networks, direct and indirect estimates are reported separately. (eTable 4,5 & eFigure 1 in
13 Supplement).
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26 Moderate certainty evidence showed that, compared to placebo, opioids provide small
27 improvements in pain (modelled RD for achieving the MID 15%, 95% CrI 13 to 17), physical
28 functioning (modelled RD for achieving the MID 5%, 95% CrI 3 to 8), and sleep quality
29 (modelled RD for achieving the MID 8%, 95% CrI 4 to 13). Low to moderate certainty evidence
30 supported similar effects for cannabis for medical use vs. placebo. Neither were more effective
31 than placebo for role, social, or emotional functioning (all high to moderate certainty evidence).
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33 (Table 2, eTable 4 &, eFigure 2-13 in Supplement).
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45 Low certainty evidence from 82 RCTs involving 19 693 patients suggested that there may be
46 little to no difference in pain relief between cannabis for medical use and opioids (WMD 0.23cm
47 on a 10cm VAS, 95% CrI -0.06 to 0.53). (Table 2, eFigure 1 & eTable 4 in Supplement).
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49 Moderate certainty evidence from 44 RCTs involving 12 727 patients shows there is probably
50 little to no difference in physical functioning with cannabis for medical use compared to opioids
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(WMD 0.47 points on the 100-point SF-36 PSC score, 95% CrI -1.97 to 2.99). (Table 2, eTable 4 in Supplement). Low certainty evidence from 32 RCTs involving 8 201 patients suggests that there may be little to no difference in sleep quality between cannabis for medical use and opioids (WMD 0.49mm on a 100mm VAS, 95% CrI -4.72 to 5.59). (Table 2, eTable 4 in Supplement). There were insufficient data to construct networks for health-related quality of life (eAppendix 4 in Supplement).

Discontinuations due to adverse events were reported in 22 enrichment trials (6 831 patients) and in 51 non-enrichment trials (13 012 patients). Among enrichment trials, low certainty evidence suggests that there may be little to no difference in discontinuations due to adverse events between cannabis for medical use and opioids (OR 0.77, 95% CrI 0.07 to 8.83). Moderate certainty evidence shows that in non-enriched studies, discontinuations due to adverse events are probably less for cannabis for medical use vs. opioids (OR 0.55, 95% CrI 0.36 to 0.83). (Table 2). Moderate and high certainty evidence showed that, compared to placebo, opioids and cannabis for medical use, respectively, probably results in higher discontinuations compared to placebo (modelled RD for achieving the MID for opioids vs. placebo, 10%, 95% CrI 8% to 12%; cannabis for medical use vs. placebo, 4%, 95% CrI 1% to 7%). (Table 2, eFigure 14-17 in Supplement).

We found no evidence of credible subgroup effects based on type of pain condition (neuropathic versus non-neuropathic), length of follow-up, sample size, or opioid dose (Table 3, eTable 6-12 in Supplement).

Table 2: Treatment effects and certainty of evidence (GRADE) for opioids and cannabis for medical use in patients with chronic noncancer pain

Comparison	Direct evidence		Indirect evidence		Network estimate WMD (95% CrI)	RD for achieving the MID (95% CI)	GRADE
	no. of trials (patients)	Treatment effect WMD* (95% CI)	no. of trials (patients)	Treatment effect WMD* (95% CI)			
Pain relief: 10cm VAS for pain; lower is better; MID = 1cm							
Opioids vs. placebo	62 (17,431)	-0.84 (-0.99 to -0.69)	62 (17,431)	-0.83 (-0.97 to -0.70)	-0.83 (-0.97 to -0.70)	15% (13% to 17%)	Moderate
Cannabis for medical use vs. placebo	19 (2,116)	-0.63 (-0.94 to -0.32)	19 (2,116)	-0.59 (-0.88 to -0.32)	-0.60 (-0.87 to -0.33)	11% (6% to 15%)	Low
Cannabis for medical use vs. opioids	1 (146)	0.13 (-0.54 to 0.80)	81 (19,547)	0.24 (-0.07 to 0.55)	0.23 (-0.06, 0.53)	-	Low
Physical functioning: 0-100 point SF-36 PCS score; higher is better; MID = 5-points							
Opioids vs. placebo	32 (10,926)	2.38 (1.05 to 3.72)	-	-	2.05 (1.01, 3.29)	5% (3% to 8%)	Moderate
Cannabis for medical use vs. placebo	12 (1,801)	3.00 (0.08 to 5.91)	-	-	2.52 (0.37, 4.91)	6% (1% to 12%)	Moderate
Cannabis for medical use vs. opioids	-	-	44 (12,727)	0.47 (-1.97 to 2.99)	0.47 (-1.97 to 2.99)	-	Moderate
Emotional functioning: 0-100 point SF-36 MCS score; higher is better; MID = 5-points							
Opioids vs. placebo	22 (7,267)	-0.00 (-1.09 to 1.09)	-	-	-0.15 (-1.10 to 0.92)	-	High
Cannabis for medical use vs. placebo	8 (1,515)	0.72 (-1.01 to 2.45)	-	-	0.70 (-1.42 to 2.84)	-	Moderate
Cannabis for medical use vs. opioids	-	-	30 (8,782)	0.85 (-1.55 to 3.18)	0.85 (-1.55 to 3.18)	-	Low
Role functioning: 0-100 point SF-36 subscale for role limitations due to physical problems; higher is better; MID = 10-points							
Opioids vs. placebo	13 (3,661)	0.91 (-1.17 to 2.98)	-	-	0.94 (-1.26 to 3.17)	-	Moderate
Cannabis for medical use vs. placebo	5 (528)	1.27 (-12.39 to 14.93)	-	-	0.88 (-3.78 to 6.05)	-	Moderate
Cannabis for medical use vs. opioids	-	-	18 (4,189)	-0.05 (-5.16 to 5.60)	-0.05 (-5.16 to 5.60)	-	Moderate
Social functioning: 0-100 point SF-36 subscale for social functioning; higher is better; MID = 10-points							
Opioids vs. placebo	14 (4,075)	0.47 (-1.47 to 2.41)	-	-	1.17 (-1.72 to 4.58)	-	Moderate
Cannabis for medical use vs. placebo	6 (795)	-1.82 (-5.79 to 2.15)	-	-	1.70 (-3.28 to 8.13)	-	Moderate
Cannabis for medical use vs. opioids	-	-	20 (4,870)	0.55 (-5.34 to 7.41)	0.55 (-5.34 to 7.41)	-	Moderate
Sleep quality: 100mm VAS for sleep quality; higher is better; MID = 100mm							
Opioids vs. placebo	21 (6,677)	5.55 (2.67 to 8.43)	-	-	5.46 (2.62 to 8.59)	8% (4% to 13%)	Moderate
Cannabis for medical use vs. placebo	11 (1,524)	6.04 (1.43 to 10.66)	-	-	5.95 (1.82 to 10.24)	9% (3% to 15%)	Low
Cannabis for medical use vs. opioids	-	-	32 (8,201)	0.49 (-4.72 to 5.59)	0.49 (-4.72 to 5.59)	-	Low
Discontinuations due to adverse events (enriched trials)							
Opioids vs. placebo	20 (6,699)	OR, 1.39 (1.04 to 1.86)	-	-	OR, 1.25 (0.91, 1.67)	-	Low

Cannabis for medical use vs. placebo	2 (132)	OR, 5.00 (0.25 to 101.7)		-	OR, 0.96 (0.09 to 10.80)		Low
Cannabis for medical use vs. opioids		-	22 (6,831)	OR, 0.77 (0.07 to 8.83)	OR, 0.77 (0.07 to 8.83)		Low
Discontinuations due to adverse events (non-enriched trials)							
Opioids vs. placebo	35 (11,019)	OR, 3.58 (3.00 to 4.27)	35 (11,019)	OR, 3.27 (2.70 to 3.93)	OR, 3.27 (2.71 to 3.90)	10% (8% to 12%)	Moderate
Cannabis for medical use vs. placebo	15 (1,801)	OR, 2.47 (1.49 to 4.11)	15 (1,801)	OR, 1.78 (1.15 to 2.63)	OR, 1.80 (1.19 to 2.63)	4% (1% to 7%)	High
Cannabis for medical use vs. opioids	1 (192)	OR, 0.50 (0.16, 1.61)	50 (12,820)	OR, 0.54 (0.34 to 0.84)	OR, 0.55 (0.36 to 0.83)		Moderate

OR = odds ratio. RD = risk difference and represents the percentage of patients achieved at or above MID. WMD = weighted mean difference

Table 3: Subgroup analysis for pain and secondary outcomes with moderate to high certainty evidence

Subgroup factors		Pain relief	Physical functioning	Role functioning	Social functioning	Discontinuations due to adverse events (non-enriched)
		WMD 95% CrI	WMD 95% CrI	WMD 95% CrI	WMD 95% CrI	OR 95% CrI
Clinical condition	Neuropathic	0.74 (0.30,1.12)	-0.67 (-4.46, 3.28)	-4.66 (-21.16,5.49)	-8.09 (-16.89,-0.69)	0.91 (0.48, 1.76)
	Non-neuropathic	-0.12 (-0.55,0.30)	0.97 (-2.67, 4.72)	9.81 (-1.55,21.10)	1.01 (-3.01,4.75)	*0.34* (0.15, 0.67)
Length of follow-u	≤ 2 months	0.04 (-0.36,0.45)	2.35 (-2.72,6.56)	8.59 (-3.64,20.37)	-0.31 (-8.27,7.79)	*0.42* (0.20, 0.79)
	>2 months	0.41 (-0.04,0.85)	-0.75 (-3.83, 2.38)	-2.48 (-11.89, 5.23)	-2.26 (-9.50,2.29)	0.65 (0.37, 1.16)
Adequate randomization	Yes	0.14 (-0.25,0.53)	0.36 (-2.14, 3.03)	2.92 (-9.96,15.78)	0.07 (-4.45,4.34)	*0.48* (0.27, 0.79)
	No	0.37 (-0.19,0.92)	0.01 (-10.42, 9.03)	-4.55 (-26.29,14.71)	-6.93 (-21.75,6.27)	0.77 (0.31, 1.86)
Adequate concealment	Yes	0.25 (-0.08,0.58)	0.87 (-1.43, 3.37)	-0.81 (-6.88,5.75)	-2.02 (-6.75,1.60)	*0.51* (0.31, 0.79)
	No	NA	NA	NA	NA	NA
Industry funded trials	Yes	0.23 (-0.13,0.58)	0.72 (-2.02, 3.52)	-0.71 (-6.86,5.72)	-0.62 (-4.94,2.69)	*0.55* (0.33, 0.92)
	No	0.32 (-0.78,1.39)	-4.57 (-15.20, 6.66)	-4.59 (-18.01,14.04)	-0.62 (-10.78,10.11)	0.77 (0.09, 3.75)
Loss to follow-up	High (≥20%)	*0.53* (0.08,0.98)	-0.39 (-5.45, 4.52)	1.40 (-3.77, 8.21)	-3.31 (-8.10,1.48)	0.63 (0.36, 1.11)
	Low (<20%)	-0.09 (-0.64,0.38)	0.86 (-3.74, 6.97)	-18.49 (-51.56,8.85)	0.32 (-17.97,13.13)	0.79 (0.13, 2.97)
Study design	Enrichment	-0.65 (-1.65,0.35)	NA	-22.92 (-61.99,16.11)	-14.19 (-40.56,12.39)	NA
	Non-enrichment	0.25 (-0.07,0.57)	0.37 (-2.57, 3.19)	0.55 (-5.34, 7.41)	-1.54 (-6.21,2.32)	

All values in bold are statistically significant at the 0.05 significance level. * = unless otherwise indicated. Results are cannabis for medical use versus opioids. Pain relief for neuropathic pain vs non-neuropathic p-value = 0.004. Social functioning for neuropathic pain vs non-neuropathic p-value = 0.047. p-value based on test of interaction. Number of studies and p-values for all comparisons are available in eTable 7 in Supplement.

Discussion

This network meta-analysis of 90 trials that enrolled 22 028 people living with chronic noncancer pain provides low certainty evidence that cannabis for medical use is similarly effective to opioids for pain relief and sleep quality, and moderate certainty evidence for similar effects on physical functioning. The magnitude of effects vs. placebo for cannabis for medical use or opioids was modest, with the modelled RD for achieving the MID for pain, function and sleep ranging from 5% to 15%. Moderate certainty evidence also suggests that use of cannabis for medical use vs. opioids resulted in fewer discontinuations due to adverse events. Moderate to high certainty evidence showed that neither opioids nor cannabis for medical use were effective for improving emotional, social or role functioning among people living with chronic pain.

Our study, which is the first network meta-analysis exploring the comparative effectiveness of cannabis for medical use and opioids for chronic noncancer pain, has several strengths. We conducted a comprehensive search strategy, including grey literature from clinicaltrials.gov, used the GRADE approach to appraise the certainty of evidence for treatment effects and followed GRADE guidance for communicate our findings. We evaluated harms using discontinuations due to adverse events to facilitate pooling across trials. Further, we explored subgroup effects and assessed their credibility according to current best practices.

Clinical guidelines for chronic noncancer pain recommend optimization of nonopioid based pharmacologic and non-pharmacologic therapies prior to initiating opioids [127-129]. However, approximately a third of all patients living with chronic noncancer pain are prescribed opioids

[130]; and increasing concerns regarding harms of long-term opioid therapy has generated enthusiasm for alternatives, including cannabis for medical use [131]. In part, because some observational studies (but not others [132,133]) have shown an association between legalization of cannabis for medical use and reduced prevalence of opioid use disorder and opioid overdose [134,135]. Although prone to measured and unmeasured confounding bias, recent observational studies and studies using registry data have also shown favourable improvements in pain and health related quality of life outcomes for cannabis for medical use when compared to opioids [136-139]. Moreover, users of cannabis for medical use acknowledge substitution of prescription medication, particularly opioids, as a common motive [140,141]. This issue is controversial [142], however, and recent guidelines have provided conflicting recommendations regarding the effectiveness of cannabis for medical use for chronic pain and whether use of cannabis reduces opioid consumption [11-13,143]. An important limitation of prior evidence syntheses is the scarcity of trials directly comparing cannabis for medical use against opioids for chronic pain. These treatment options are mostly trialed against placebo, and network meta-analysis can therefore establish comparative effectiveness by virtue of this common compactor. Our findings suggest that both opioids and cannabis for medical use may provide benefits for a minority of chronic pain patients (e.g., compared to placebo, 10-15% of patients experience a 1cm or greater relief in pain on a 10cm scale). However, reviews of patient values and preferences show that people living with chronic pain place high value on the possibility of achieving small but important pain relief [144,145]. Furthermore, cannabis does not cause respiratory depression which can result from opioids consumption and lead to non-fatal or fatal overdose [146].

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3 Future research should directly compare the effectiveness of opioids vs. cannabis for chronic
4 pain, and follow patients sufficiently to inform long-term benefits and harms. Trials should
5 report all outcomes measures of importance to people who live with chronic pain [18,19 ,147].
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7 Randomized trials are also needed to establish opioid-substitution effects of cannabis for chronic
8 pain, and observational studies to inform long-term and infrequent harms of both cannabis for
9 medical use and opioids for chronic pain (e.g., overdose, addiction).
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19 There are some limitations associated with our study. None of the trials eligible for our review
20 explored inhaled cannabis, and our results may not be generalizable to this method of
21 administration. We excluded trials with combination drugs because results may be confounded
22 by the additional drugs. As such, our results may not reflect outcomes where opioids or cannabis
23 are used in combination with other drugs (e.g. tramadol and acetaminophen). The cannabis plant
24 contains over 500 chemical substances and the main cannabinoids included in most RCTs are
25 THC, CBD, or THC/CBD and not the full plant. We pooled different opioids and types of
26 cannabis for medical use that may not be common forms of products used in the real-world;
27 however, subgroup analysis suggests that effects for chronic pain are similar across different
28 opioids and cannabis for medical use products [148,149]. Further, a network meta-analysis found
29 no evidence to support important differences in pain relief, functional improvement,
30 or gastrointestinal adverse events between different types of opioids [148]. In order to facilitate
31 pooling, we reported harms as discontinuations due to adverse events instead of reporting
32 specific adverse events experienced by trial participants. In other meta-analyses of RCTs,
33 cannabis for medical use was associated with greater central nervous system and gastrointestinal
34 adverse events, versus placebo [149,150]. Both opioids and cannabis for medical use can result
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3 in use disorders [151,152] while opioids can also result in fatal and non-fatal overdose; however,
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5 we were unable to construct a network to explore the comparative risk of these important harms
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7 as RCTs are poorly suited to detect rare harms or harms that take a while to manifest. We do not
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9 feel our analysis suffers from serious intransitivity as the distribution of potential effect
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11 modifiers were well balanced across the included studies [153]. Our results for opioids may be
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13 overestimated due to small study effects from the included RCTs for pain relief, physical
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15 functioning and sleep and for pain relief in the cannabis RCTs.
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Conclusions

In this network meta-analysis of randomized trials of patients with chronic noncancer pain, low to moderate certainty evidence suggests that cannabis for medical use may provide similarly small improvements in pain, physical function, and sleep compared to opioids, and fewer discontinuations due to adverse events.

For peer review only

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3 **Contributors:** HMJ, JWB, BS, ML and JET conceived and designed the study. HMJ, LW, AN
4 and RJC acquired the data. HMJ, JWB, BS and MZ contributed to the statistical analyses. HMJ
5 performed the statistical analyses. All authors interpreted the data and could access data included
6 in the study. HMJ, JWB and JET drafted the manuscript. All authors made critical revisions to
7 the article for important intellectual content and gave final approval for the article.
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17 **Competing interests:** None declared.
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23 **Ethical approval:** Not required.
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49 **Transparency:** The lead authors affirm that the manuscript is an honest, accurate, and
50 transparent account of the study being reported; that no important aspects of the study have been
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3 omitted; and that any discrepancies from the study as originally planned (and, if relevant,
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5 registered) have been explained.
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5 **Figure 1: Study Selection Process for the Systematic Review and Network Meta-Analysis**

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7 **Figure 2: Evidence Network for Network Meta-Analysis Outcomes**

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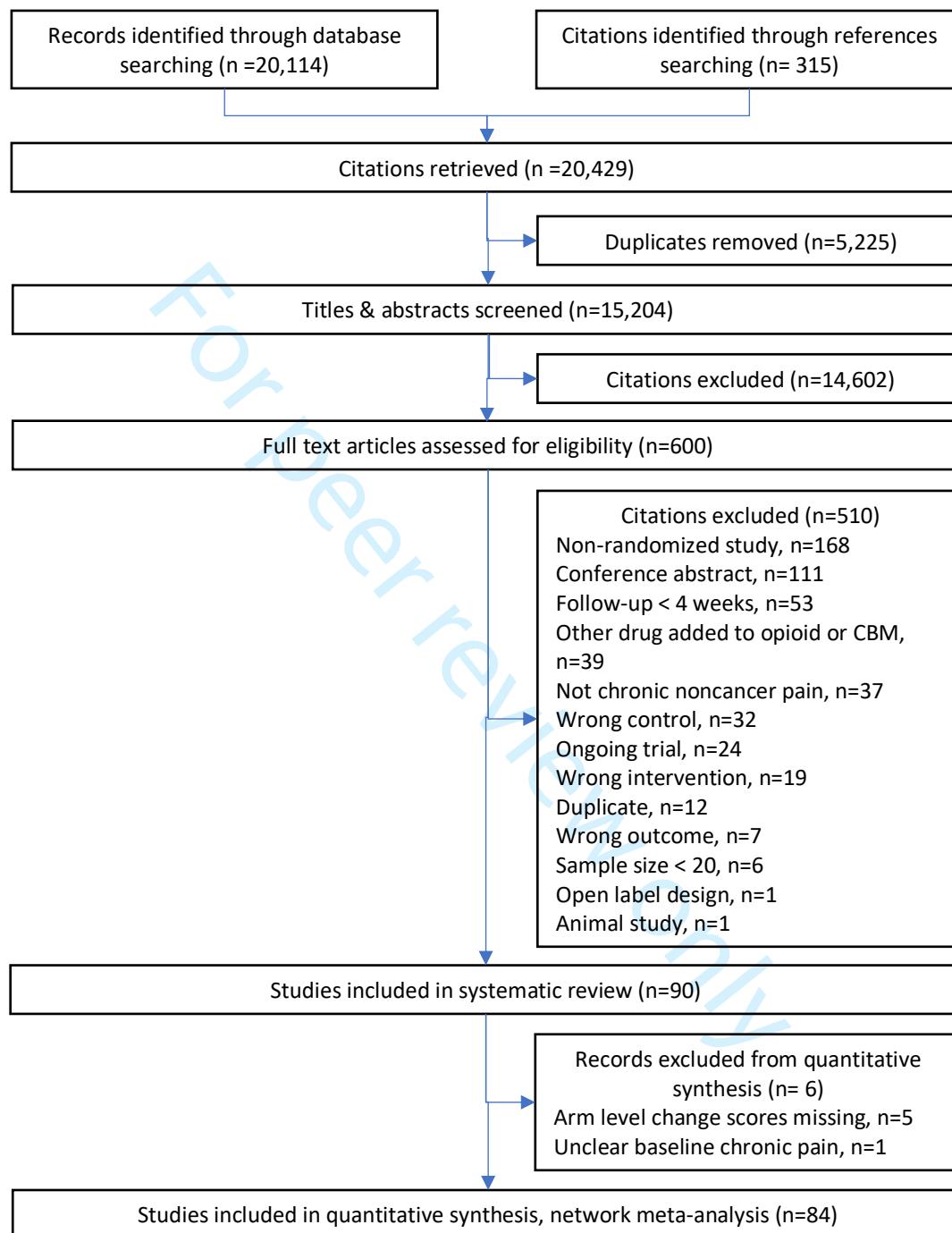
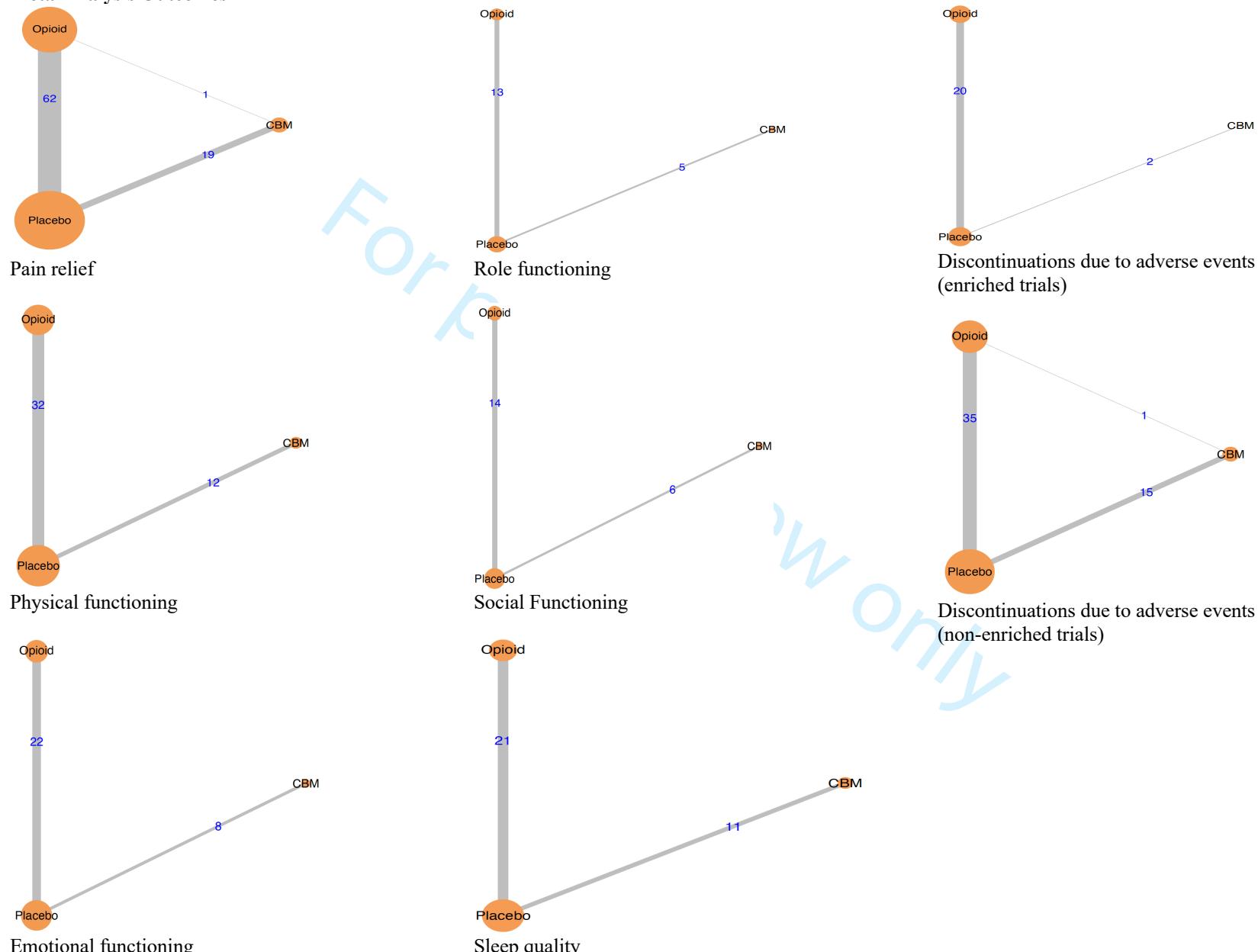
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For peer review only

eAppendix 1: Literature search strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Search Strategy:

1 (chronic adj4 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word,
2 keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique
3 identifier, synonyms] (58120)
4 2 Chronic Pain/ (9487)
5 3 exp Osteoarthritis/ (54546)
6 4 osteoarthritis*.mp. (75997)
7 5 osteo-arthritis.mp. (367)
8 6 degenerative arthrit*.mp. (1219)
9 7 exp Arthritis, Rheumatoid/ (104666)
10 8 exp Neuralgia/ (17706)
11 9 Diabetic Neuropathies/ (13601)
12 10 (neuropath* adj5 (pain* or diabet*)).mp. (36937)
13 11 neuralg*.mp. (23772)
14 12 zoster.mp. (19225)
15 13 Irritable Bowel Syndrome/ (6066)
16 14 (IBS or irritable colon or irritable bowel).mp. (14347)
17 15 Migraine Disorders/ (23014)
18 16 migraine.mp. (34507)
19 17 Fibromyalgia/ (7573)
20 18 fibromyalg*.mp. (10324)
21 19 complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ (5219)
22 20 (complex regional pain syndromes or causalgia).mp. (2139)
23 21 Pain, Intractable/ (6021)
24 22 Phantom Limb/ (1737)
25 23 Hyperalgesia/ (10026)
26 24 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (16519)
27 25 or/1-24 (374187)
28 26 exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ (34838)
29 27 Radiculopathy/ or radiculopathy.mp. (8057)
30 28 musculoskeletal pain/ or headache/ (27891)
31 29 exp Arthralgia/ (10991)
32 30 exp Headache Disorders/ (31166)
33 31 headache*.mp. (83353)
34 32 Temporomandibular Joint Dysfunction Syndrome/ (4838)
35 33 ((TMJ or TMJD) and pain*).mp. (2434)
36 34 whiplash.mp. or exp whiplash injury/ (3756)
37 35 exp Cumulative Trauma Disorders/ (12612)
38 36 exp Peripheral Nervous System Diseases/dt [Drug Therapy] (12959)
39 37 Pain Measurement/de [Drug Effects] (6352)
40 38 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi*
41 or myodyn* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (39779)
42 39 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint*
43 or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or
44 cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (144063)
45 40 or/26-39 (299548)
46 41 (acute or emergency or preoperative or postoperative).ti,ab. (1700816)
47 42 40 not 41 (252546)
48 43 25 or 42 (532409)
49 44 exp Analgesics, Opioid/ (103616)
50 45 (opioid* or opiate*).mp. (114059)
51 46 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or

1
2
3 dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or
4 ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or
5 levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine
6 or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or
7 promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.(143753)
8 47 or/44-46 (199233)
9 48 exp Narcotics/ (111500)
10 49 narcotic*.mp. (57165)
11 50 (adolonta or Anpec or Ardinex or Asimadoline or Alvimapam or amadol or biodalge or biokanol or Codinovo
12 or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or
13 dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or
14 duromorph or duragesic or durogesic or eucodal or Fedotzine or Fenantest or Fentora or Fortral or Hycodan or
15 Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or
16 isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or
17 lexir or lidol or lydol or morfin or morphine or morphin or morphinium or morphinene or morphium or ms
18 contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or
19 oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or
20 skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or
21 tramadolhameln or tramadol or tramadura or tramagetic or tramagit or tramal or tramex or tramundin
22 or trasedal or theradol or tiral or topalge or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin
23 or tramadoc or ultram or zamudol or zumalge or zyadol or zytram).mp. [mp=title, abstract, original title, name of
24 substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease
supplementary concept word, unique identifier, synonyms] (9563)
25 51 or/44-50 (227775)
26 52 43 and 51 (22678)
27 53 epidemiologic studies/ (7641)
28 54 exp Case-Control Studies/ (904344)
29 55 exp Cohort Studies/ (1723417)
30 56 Case control.tw. (106622)
31 57 (cohort adj (study or studies)).tw. (151570)
32 58 Cohort analy\$.tw. (6083)
33 59 (Follow up adj (study or studies)).tw. (44718)
34 60 ((observational or epidemiol*) adj (study or studies)).tw. (156420)
35 61 Longitudinal.tw. (201362)
36 62 Retrospective.mp. or prospective.tw. (1247587)
37 63 Cross sectional.tw. (272577)
38 64 Cross-sectional studies/ (260504)
39 65 or/53-64 (2717825)
40 66 exp animals/ not humans.sh. (4438182)
41 67 65 not 66 (2649950)
42 68 52 and 67 (3763)
43 69 randomized controlled trial.pt. (456617)
44 70 controlled clinical trial.pt. (92277)
45 71 randomized.ab. (406479)
46 72 placebo.ab. (187496)
47 73 drug therapy.fs. (2003496)
48 74 randomly.ab. (287373)
49 75 trial.ab. (422125)
50 76 groups.ab. (1777409)
51 77 or/69-76 (4167722)
52 78 clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs. (5199787)
53 79 randomized controlled trial.pt. or randomized controlled trial.mp. (476635)
54 80 randomized controlled trial.pt. or randomized.mp. or placebo.mp. (790362)
55 81 or/78-80 (5214838)
56 82 77 or 81 (6680171)
57 83 exp animals/ not humans.sh. (4438182)

1
2
3 84 82 not 83 (5604099)
4 85 43 and 51 and 84 (14496)
5 86 limit 85 to yr="2010 -Current" (6438)
6 87 68 or 86 (8377)
7 88 (MEDLINE or systematic review or literature search).tw. or meta analysis.mp,pt. (256038)
8 89 43 and 51 and 88 (881)
9 90 87 or 89 (8697)
10 91 exp Sleep Apnea Syndromes/ (30607)
11 92 sleep apn?ea.mp. (38637)
12 93 sleep-disordered breathing.mp. (5685)
13 94 hypogonadism.mp. or Hypogonadism/ (13040)
14 95 ((testosterone or androgen) and (deprivation or deficiency)).mp. (12336)
15 96 OPIAD.mp. (10)
16 97 or/91-96 (64161)
17 98 52 and 97 (144)
18 99 90 or 98 (8736)

19 **PsycInfo**

20 **Database: PsycINFO via OVID**

21 Search Strategy:

22 1 (chronic adj4 pain*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests &
23 measures] (19944)
24 2 chronic pain/ (12078)
25 3 exp arthritis/ (3853)
26 4 osteoarthrit*.mp. (1758)
27 5 osteo-arthritis.mp. (8)
28 6 degenerative arthrit*.mp. (15)
29 7 exp neuralgia/ (892)
30 8 exp neuropathy/ (5931)
31 9 (neuropath* adj5 (pain* or diabet*)).mp. (6256)
32 10 neuralg*.mp. (1530)
33 11 zoster.mp. (550)
34 12 irritable bowel syndrome/ (1055)
35 13 (IBS or irritable colon or irritable bowel).mp. [mp=title, abstract, heading word, table of contents, key
36 concepts, original title, tests & measures] (1832)
37 14 migraine headache/ (8772)
38 15 migraine.mp. (11715)
39 16 fibromyalgia/ (1768)
40 17 fibromyalg*.mp. (3042)
41 18 complex regional pain syndromes.mp. (55)
42 19 "complex regional pain syndrome (type i)"/ (137)
43 20 (complex regional pain syndromes or causalgia).mp. (109)
44 21 somatosensory disorders/ (1266)
45 22 hyperalgesi*.mp. (3914)
46 23 somatoform pain disorder/ (801)
47 24 somatoform disorders/ (7528)
48 25 conversion disorder/ (998)
49 26 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (3008)
50 27 or/1-26 (58879)
51 28 back pain.mp. or exp Back Pain/ (5353)
52 29 radiculopathy.mp. (202)
53 30 musculoskeletal pain.mp. (1410)
54 31 Arthralgia.mp. (105)
55 32 headache.mp. or exp HEADACHE/ (19164)
56 33 ((TMJ or TMJD) and pain*).mp. (142)
57 34 WHIPLASH/ or whiplash.mp. (571)

1
2
3 35 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi*
4 or myodyn* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (5452)
5 36 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint*
6 or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or
7 cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (18302)
8 37 or/28-36 (39808)
9 38 (acute or emergency or preoperative or postoperative).ti,ab. (111436)
10 39 37 not 38 (35095)
11 40 27 or 39 (71492)
12 41 exp opiates/ (22978)
13 42 (opioid* or opiate*).mp. (27750)
14 43 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or
15 dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or
16 ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or
17 levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine
18 or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or
19 promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (27830)
20 44 exp narcotic drugs/ (27031)
21 45 narcotic*.mp. (5729)
22 46 (adolonta or Anpec or Ardinex or Asimadoline or Alvimapam or amadol or biodaligic or biokanol or Codinovo
23 or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or
24 dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or
25 duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or
26 Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or
27 isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or
28 lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms
29 contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or
30 oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or
31 skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or
32 tramadolhameln or tramadol or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin
33 or trasedal or theradol or tiral or topalgeic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin
34 or tramadoc or ultram or zamudol or zumalgec or zydol or zytram).mp. (928)
35 47 or/41-46 (47945)
36 48 37 and 47 (2028)
37 49 animals/ not humans/ (7067)
38 50 animal models/ (29760)
39 51 animal research/ (368)
40 52 exp rodents/ (201732)
41 53 (rat or rats or mouse or mice).ti. (110418)
42 54 or/49-53 (226624)
43 55 48 not 54 (1547)

Database: AMED (Allied and Complementary Medicine) via OVID

Search Strategy:

1 analgesics opioid/ (335)
2 (opioid* or opiate*).mp. (1449)
3 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or
4 dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or
5 ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or
6 levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine
7 or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or
8 promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. [mp=abstract, heading words,
title] (1097)
9 4 narcotics/ (177)
10 5 narcotic*.mp. (345)
11 6 (adolonta or Anpec or Ardinex or Asimadoline or Alvimapam or amadol or biodaligic or biokanol or Codinovo

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2
3 or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or
4 dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or
5 duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or
6 Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or
7 isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or
8 lexit or lidol or lydol or morfin or morphia or morphin or morphinium or morphinene or morphium or ms
9 contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or
10 oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or
11 skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or
12 tramadolhameln or tramadol or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin
13 or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin
14 or tramadoc or ultram or zamudol or zumalgie or zydol or zytram).mp. [mp=abstract, heading words, title] (109)
15 7 or/1-6 (2268)
16 8 (chronic adj4 pain).mp. [mp=abstract, heading words, title] (4640)
17 9 exp arthritis/ (5636)
18 10 arthralgia/ (189)
19 11 fibromyalgia/ (1656)
20 12 neuralgia/ (157)
21 13 diabetic neuropathies/ (264)
22 14 (neuropath* adj5 (pain* or diabet*)).mp. (981)
23 15 neuralg*.mp. [mp=abstract, heading words, title] (335)
24 16 osteoarthrit*.mp. [mp=abstract, heading words, title] (3321)
25 17 irritable bowel syndrome/ (133)
26 18 (IBS or irritable colon or irritable bowel).mp. [mp=abstract, heading words, title] (297)
27 19 fibromyalg*.mp. [mp=abstract, heading words, title] (1846)
28 20 Migraine/ or migraine.mp. (651)
29 21 complex regional pain syndromes/ or reflex sympathetic dystrophy/ (188)
30 22 (complex regional pain syndromes or causalgia).mp. [mp=abstract, heading words, title] (77)
31 23 pain intractable/ (431)
32 24 hyperalgesia/ or phantom limb/ (181)
33 25 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. [mp=abstract,
34 heading words, title] (675)
35 26 or/8-25 (15230)
36 27 exp backache/ (6186)
37 28 radiculopathy.mp. (290)
38 29 exp Headache/ or headache.mp. (1709)
39 30 Temporomandibular joint syndrome/ (67)
40 31 ((TMJ or TMJD) and pain*).mp. (28)
41 32 Whiplash injuries/ or whiplash.mp. (594)
42 33 repetition strain injury/ (312)
43 34 (backache* or backpain* or dorsalmgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi*
44 or myodyn* or neuralg* or ischialg* or crps or rachialg*).ab,ti. (2429)
45 35 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint*
46 or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or
47 cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (12871)
48 36 or/27-35 (17684)
49 37 (acute or emergency or preoperative or postoperative).ti,ab. (12782)
50 38 36 not 37 (16319)
51 39 26 or 38 (25280)
52 40 7 and 39 (532)
53 41 (rat or rats or mouse or mice).ti. (5925)
54 42 animals/ not humans/ (7083)
55 43 exp Rodents/ (8142)
56 44 41 or 42 or 43 (10161)
57 45 40 not 44 (512)
58 59
60

Central (Cochrane Library via Wiley)

1
2
3 Description:
4 ID Search Hits
5 #1 chronic near/3 pain 9973
6 #2 MeSH descriptor: [Chronic Pain] explode all trees 1178
7 #3 MeSH descriptor: [Osteoarthritis] explode all trees 4754
8 #4 osteoarthrit* 10561
9 #5 osteo-arthritis 69
10 #6 degenerative arthrit* 359
11 #7 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees 4858
12 #8 MeSH descriptor: [Neuralgia] explode all trees 1049
13 #9 MeSH descriptor: [Diabetic Neuropathies] explode all trees 1397
14 #10 neuropath* near/5 (pain* or diabet*) 4465
15 #11 neuralg* 1913
16 #12 zoster 1641
17 #13 MeSH descriptor: [Irritable Bowel Syndrome] explode all trees 674
18 #14 irritable (colon or bowel) 2448
19 #15 IBS 1629
20 #16 MeSH descriptor: [Migraine Disorders] explode all trees 1959
21 #17 migraine 4659
22 #18 MeSH descriptor: [Fibromyalgia] explode all trees 851
23 #19 fibromyalg* 1987
24 #20 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees 238
25 #21 complex regional pain syndromes or causalgia 203
26 #22 MeSH descriptor: [Pain, Intractable] explode all trees 273
27 #23 MeSH descriptor: [Phantom Limb] explode all trees 75
28 #24 MeSH descriptor: [Hyperalgesia] explode all trees 454
29 #25 ((noncancer* or non-cancer* or chronic* or recurrent or persist* or non-malign*) near/3 pain) 2107
30 #26 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 40797
31 #27 MeSH descriptor: [Back Pain] explode all trees 3879
32 #28 MeSH descriptor: [Radiculopathy] explode all trees 303
33 #29 MeSH descriptor: [Musculoskeletal Pain] explode all trees 478
34 #30 MeSH descriptor: [Arthralgia] explode all trees 1313
35 #31 MeSH descriptor: [Headache Disorders] explode all trees 2415
36 #32 MeSH descriptor: [Headache] explode all trees 1798
37 #33 headache* 26942
38 #34 MeSH descriptor: [Temporomandibular Joint Dysfunction Syndrome] explode all trees 179
39 #35 ((TMJ or TMJD) and pain*) 266
40 #36 MeSH descriptor: [Whiplash Injuries] explode all trees 208
41 #37 whiplash 460
42 #38 MeSH descriptor: [Cumulative Trauma Disorders] explode all trees 668
43 #39 backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or
fibromyalgi* or myodyn* or neuralgi* or ischialgi* or crps or rachialgi* 13481
44 #40 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or
joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or
cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) near/3 pain) 28955
45 #41 radiculopathy 893
46 #42 #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41
60275
47 #43 acute or emergency or preoperative or postoperative 200646
48 #44 42 not 43 59058
49 #45 #26 or #44 97623
50 #46 opioid* or opiate* 17932
51 #47 narcotic* 6752
52 #48 MeSH descriptor: [Analgesics, Opioid] explode all trees 6462
53 #49 MeSH descriptor: [Narcotics] explode all trees 7246
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#50 alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol 32420
#51 adolonta or Anpec or Ardinex or Asimadoline or Alvimapam or amadol or biodaligic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydronal or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgc or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgc or zydol or zytram 5622
#52 #46 or #47 or #48 or #49 or #50 or #51 42294
#53 #45 and #52 2656

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Search Strategy:

- 1 Cannabis/ (11443)
- 2 exp cannabinoids/ or cannabidiol/ or cannabinol/ or dronabinol/ (16399)
- 3 Endocannabinoids/ (6489)
- 4 exp Receptors, Cannabinoid/ (10396)
- 5 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetrabenex or sativex or endocannabinoid*).mp. (64927)
- 6 or/1-5 (64927)
- 7 pain*.mp.jw. or Pain/ (890667)
- 8 exp Osteoarthritis/ or exp Arthritis, Rheumatoid/ or exp Neuralgia/ or Diabetic Neuropathies/ or Irritable Bowel Syndrome/ or Migraine Disorders/ or Fibromyalgia/ or complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ or Pain, Intractable/ or chronic pain/ or Phantom Limb/ or Hyperalgesia/ or exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ or Radiculopathy/ or musculoskeletal pain/ or headache/ or exp Arthralgia/ or exp Headache Disorders/ or Temporomandibular Joint Dysfunction Syndrome/ or exp whiplash injury/ or exp Cumulative Trauma Disorders/ or exp Peripheral Nervous System Diseases/dt or Pain Measurement/de (423216)
- 9 ((irrita* or inflam*) adj4 (bowel or colon)).mp. (81237)
- 10 (osteoartrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*).mp. (827784)
- 11 Muscle Spasticity/ (9871)
- 12 Muscle Hypertonia/ (1033)
- 13 (spasticity or spasm or spastic or hypertonia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (56343)
- 14 or/7-13 (1660232)

1
2
3 15 6 and 14 (6752)
4 16 random:.tw. or placebo:.mp. or double-blind:.tw. (1409704)
5 17 ((treatment or control) adj3 group*).ab. (680082)
6 18 (allocat* adj5 group*).ab. (29935)
7 19 ((clinical or control*) adj3 trial).ti,ab,kw. (333663)
8 20 or/16-19 (1961120)
9 21 randomized controlled trial.pt. (561669)
10 22 controlled clinical trial.pt. (94744)
11 23 clinical trials as topic.sh. (199529)
12 24 randomly.ab. (378041)
13 25 trial.ti. (258476)
14 26 drug therapy.fs. (2458509)
15 27 or/16-26 (4232754)
16 28 15 and 27 (3200)
17 29 animals/ not humans/ (4940789)
18 30 28 not 29 (2513)

EMBASE (OVID)

Search Strategy:

1 cannabis/ (39161)
2 exp cannabinoid/ (76903)
3 medical cannabis/ (3242)
4 exp cannabinoid receptor/ (16300)
5 exp endocannabinoid/ (10122)
6 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetrabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (101727)
7 or/1-6 (103167)
8 pain/ or pain*.mp. (1523452)
9 chronic pain/ or exp osteoarthritis/ or exp rheumatoid arthritis/ or exp neuralgia/ or diabetic neuropathy/ or irritable colon/ or exp migraine/ or fibromyalgia/ or intractable pain/ or agnosia/ or exp radiculopathy/ or musculoskeletal pain/ or exp arthralgia/ or headache/ or temporomandibular joint disorder/ or whiplash injury/ or exp cumulative trauma disorder/ (947642)
10 (osteoartrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (1588678)
11 ((irrita* or inflam*) adj4 (bowel or colon)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (143101)
12 muscle hypertonia/ or spasticity/ (29975)
13 (spasticity or spasm or spastic or hypertonia).mp. (102572)
14 or/8-13 (2856349)
15 7 and 14 (15652)
16 clinical article/ (2840832)
17 exp clinical study/ (11038373)
18 clinical trial/ (1030530)
19 controlled study/ (8707614)
20 randomized controlled trial/ (700351)

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2
3 21 major clinical study/ (4407914)
4 22 double blind procedure/ (193251)
5 23 multicenter study/ (318443)
6 24 single blind procedure/ (45524)
7 25 phase 3 clinical trial/ (59538)
8 26 phase 4 clinical trial/ (4691)
9 27 crossover procedure/ (69709)
10 28 placebo/ (378215)
11 29 or/16-28 (15939371)
12 30 allocat\$.mp. (195320)
13 31 assign\$.mp. (446472)
14 32 blind\$.mp. (548005)
15 33 (clinic\$ adj25 (study or trial)).mp. (7617865)
16 34 compar\$.mp. (9098845)
17 35 control\$.mp. (12329430)
18 36 cross?over.mp. (108597)
19 37 factorial\$.mp. (69675)
20 38 follow?up.mp. (50719)
21 39 placebo\$.mp. (491115)
22 40 prospectiv\$.mp. (1372469)
23 41 random\$.mp. (2010437)
24 42 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).mp. (348231)
25 43 trial.mp. (2377246)
26 44 (versus or vs).mp. (2518554)
27 45 or/30-44 (19623398)
28 46 29 and 45 (12865583)
29 47 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or
30 nonhuman/ (30266244)
31 48 human/ or normal human/ or human cell/ (23473918)
32 49 47 and 48 (23405621)
33 50 47 not 49 (6860623)
34 51 46 not 50 (10162086)
35 52 randomized controlled trial.pt. or randomi?ed.mp. or placebo.mp. (1559060)
36 53 ((treatment or control) adj3 group*).ab. (985064)
37 54 (allocat* adj5 group*).ab. (39102)
38 55 ((clinical or control*) adj3 trial).ti,ab,kw. (472392)
39 56 52 or 53 or 54 or 55 (2453456)
40 57 15 and 51 (5650)
41 58 15 and 56 (2581)
42 59 57 or 58 (6324)

43 **AMED (OVID)**

44 **Database: AMED (Allied and Complementary Medicine)**

45 Search Strategy:

46 1 exp cannabis/ (250)
47 2 cannabinoids/ (59)
48 3 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or
49 hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or
50 cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or
51 nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or
52 sativex or endocannabinoid*).mp. [mp=abstract, heading words, title] (434)
53 4 or/1-3 (434)
54 5 pain.mp. or Pain/ (35918)
55 6 exp arthritis rheumatoid/ or exp osteoarthritis/ (5358)
56 7 exp pain/ or neuralgia/ (23893)

1
2
3 8 exp diabetic neuropathies/ (1040)
4 9 irritable bowel syndrome/ (199)
5 10 Migraine/ (513)
6 11 fibromyalgia/ or myofascial pain syndromes/ or temporomandibular joint syndrome/ (2280)
7 12 complex regional pain syndromes/ or reflex sympathetic dystrophy/ (197)
8 13 Phantom limb/ (134)
9 14 hyperalgesia/ (74)
10 15 whiplash injuries/ (546)
11 16 repetition strain injury/ (324)
12 17 (osteoarthritis* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or
13 fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalg* or arthralgi* or
14 polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or
15 crohn* or colitis* or enteritis* or ileitis*).mp. (18652)
16 18 ((irrita* or inflam*) adj4 (bowel or colon)).mp. (585)
17 19 Muscle spasticity/ (1183)
18 20 Muscle hypertonia/ (84)
19 21 (spasticity or spasm or spastic or hypertonia).mp. [mp=abstract, heading words, title] (2678)
20 22 or/5-21 (50501)
21 23 4 and 22 (118)

22
23 **PsycInfo (OVID)**

24 **Database: APA PsycInfo**

25 Search Strategy:

26
27 1 exp cannabis/ or exp cannabinoids/ or tetrahydrocannabinol/ (15070)
28 2 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or
29 hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or
30 cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or
31 nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetrabinex or
32 sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title,
33 tests & measures, mesh word] (30531)
34 3 1 or 2 (30531)
35 4 pain*.mp. or exp PAIN/ (140896)
36 5 (osteoarthritis* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or
37 fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalg* or arthralgi* or
38 polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or
39 crohn* or colitis* or enteritis* or ileitis*).mp. [mp=title, abstract, heading word, table of contents, key concepts,
40 original title, tests & measures, mesh word] (74571)
41 6 4 or 5 (180976)
42 7 3 and 6 (2094)
43 8 limit 7 to "therapy (best balance of sensitivity and specificity)" (372)
44 9 (double-blind or random: assigned or control).tw. (522132)
45 10 clinical trials/ (12034)
46 11 (controlled adj3 trial*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title,
47 tests & measures, mesh word] (58491)
48 12 (clinical adj2 trial*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests
49 & measures, mesh word] (50934)
50 13 (randomi?ed adj7 trial*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title,
51 tests & measures, mesh word] (69435)
52 14 or/9-13 (589510)
53 15 7 and 14 (525)
54 16 8 or 15 (525)
55 17 muscle spasms/ (522)
56 18 (spasticity or spasm or spastic or hypertonia).mp. [mp=title, abstract, heading word, table of contents, key
57 concepts, original title, tests & measures, mesh word] (5660)

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3 19 17 or 18 (5767)
4 20 3 and 19 (129)
5 21 limit 20 to "therapy (best balance of sensitivity and specificity)" (36)
6 22 14 and 20 (80)
7 23 21 or 22 (80)
8 24 16 or 23 (548)
9
10 Cochrane Library (Wiley)

11 ID Search Hits
12 #1 MeSH descriptor: [Cannabis] 1 tree(s) exploded 10
13 #2 MeSH descriptor: [Cannabinoids] explode all trees 928
14 #3 MeSH descriptor: [Endocannabinoids] explode all trees 63
15 #4 MeSH descriptor: [Endocannabinoids] explode all trees 63
16 #5 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah
17 or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or
18 cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or
19 nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or
20 sativex or endocannabinoid*):ti,ab,kw (Word variations have been searched) 5386
21 #6 #1 or #2 or #3 or #4 or #5 5386
22 #7 MeSH descriptor: [Pain] explode all trees 54054
23 #8 (pain*):ti,ab,kw (Word variations have been searched) 207177
24 #9 #7 or #8 213544
25 #10 #6 and #9 794
26 #11 [mh Osteoarthritis] or [mh ^"Arthritis, Rheumatoid"] or [mh Neuralgia] or [mh ^"Diabetic Neuropathies"]
27 or [mh ^"Irritable Bowel Syndrome"] or [mh ^"Migraine Disorders"] or [mh Fibromyalgia] or [mh ^"complex
28 regional pain syndromes"] or [mh causalgia] or [mh ^"reflex sympathetic dystrophy"] or [mh ^"pain Intractable"] or
29 [mh ^"Phantom Limb"] or [mh Hyperalgesia] or [mh ^"back pain"] or [mh ^"failed back surgery syndrome"] or [mh
30 ^"low back pain"] or [mh Radiculopathy] or [mh ^"musculoskeletal pain"] or [mh headache] or [mh Arthralgia] or
31 [mh ^"Headache Disorders"] or [mh ^"Temporomandibular Joint Dysfunction Syndrome"] or [mh ^"whiplash
32 injury"] or [mh ^"Cumulative Trauma Disorders"] or [mh "Peripheral Nervous System Diseases"/DT] or [mh ^"Pain
33 Measurement"/DE] 35211
34 #12 (osteoarthrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache*
35 or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or
36 polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or
37 crohn* or colitis* or enteritis* or ileitis*) 126119
38 #13 (irrita* or inflam*) near/4 (bowel or colon) 8688
39 #14 #11 or #12 or #13136956
40 #15 #6 and #14 513
41 #16 #10 or #15 in Trials 909
42 #17 MeSH descriptor: [Muscle Spasticity] explode all trees 999
43 #18 MeSH descriptor: [Muscle Hypertonia] explode all trees 1118
44 #19 spasticity or spasm or spastic or hypertonia 8777
45 #20 #17 or #18 or #198841
46 #21 #20 and #6 198
47 #22 #10 or #15 or #21 in Trials1001
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54 CINAHL (EBSCO)
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#	Query	Results
S51	S49 OR S50	849
S50	S48	427
S49	S29 AND S48	721
S48	S4 AND S47	2,847
S47	S7 OR S36 OR S46	580,420
S46	S43 OR S44 OR S45	14,915
S45	TX spasticity or spasm or spastic or hypertonia (MH "Muscle Hypertonia")	14,915
S44	(MH "Muscle Spasticity")	517
S43	S31 OR S41	802
S42	S39 OR S40	169
S41	S29 AND S38	154
S40	S38	49
S39	S37 NOT S8	464
S38	S4 AND S36	2,025
S37	S32 OR S33 OR S34 OR S35	458,156
S36	(irrita* or inflam*) N4 (bowel or colon)	18,662
S35	TX (osteoarthritis* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*)	269,583
S34	(MH Pain+) OR (MH Phantom Limb) OR (MH Hyperalgesia) OR (MH back pain+) OR (MH "failed back surgery syndrome+") OR (MH "low back pain+") OR (MH Radiculopathy) OR (MH "musculoskeletal pain") OR (MH headache) OR (MH Arthralgia+) OR (MH "Headache Disorders+") OR (MH "Temporomandibular Joint Dysfunction Syndrome") OR (MH "whiplash injury+/" OR (MH "Cumulative Trauma Disorders+"))	226,279
S33	TX (MH Osteoarthritis+) OR (MH "Arthritis, Rheumatoid+") OR (MH Neuralgia) OR (MH Diabetic Neuropathies) OR (MH "Irritable Bowel Syndrome") OR (MH "Migraine Disorders") OR (MH Fibromyalgia) OR (MH "complex regional pain syndromes") OR (MH causalgia+) OR (MH "reflex sympathetic dystrophy+")	85,767
S32	S9 OR S30	633

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2			
3	S30	S8 AND S29	526
4	S29	S16 OR S21 OR S28	1,384,715
5	S28	S22 OR S23 OR S24 OR S25 OR S26 OR S27	1,181,925
6	S27	(MH "Prospective Studies+")	495,834
7	S26	(MH "Evaluation Research+")	330,364
8	S25	(MH "Comparative Studies")	426,809
9	S24	"latin square"	248
10	S23	(MH "Study Design") OR (MH "Crossover Design") OR (MH "Experimental Studies+")	423,651
11	S22	(MH "Random Sample+")	116,667
12	S21	S17 OR S18 OR S19 OR S20	493,219
13	S20	"random*"	475,828
14	S19	"placebo*"	73,590
15	S18	(MH "Placebos")	13,285
16	S17	(MH "Placebo Effect")	2,426
17	S16	S10 OR S11 OR S12 OR S13 OR S14 OR S15	455,728
18	S15	"triple-blind"	489
19	S14	"single-blind"	17,122
20	S13	"double-blind"	63,811
21	S12	clinical W3 trial	278,173
22	S11	"randomi?ed controlled trial*"	200,563
23	S10	(MH "Clinical Trials+")	333,661
24	S9	S4 AND S7	344
25	S8	S4 AND S7	2,279
26	S7	S5 OR S6	364,720
27	S6	"pain"	342,481
28	S5	(MH "Pain+")	223,572
29	S4	S1 OR S2 OR S3	24,367
30	S3	Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or	24,367
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	tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or тетранабинекс or sativex or endocannabinoid*	
6	S2 (MH "Medical Marijuana")	2,127
8	S1 (MH "Cannabis")	10,569

PubMed

Search: (((((((pain* OR spasticity OR spasm OR spastic OR hypertonia OR osteoarthrit* OR osteo-arthritis OR arthrit* OR neuropath* OR neuralgi* OR zoster* OR migraine* OR headache* OR fibromyalgi* OR causalgia OR radiculopathy* OR whiplash OR backache* OR backpain* OR dorsalgi* OR arthralgi* OR polyarthralgi* OR arthrodyni* OR myalgi* OR myodyn* OR ischialgi* OR crps OR brachialgia *or tmj OR tmjd OR IBS OR crohn* OR colitis* OR enteritis* OR ileitis*)) AND ((trial* OR random*))) AND ((cannabis OR cannabinol OR cannabinoid* OR cannabidiol OR bhang OR hashish OR hemp OR marihuana OR marijuana OR nabilone OR cesamet OR tetrahydrocannabinol OR dronabinol OR levonantradol OR nabiximols OR palmidrol OR tetrahydrocannabinolic OR sativex OR endocannabinoid*)))) AND ((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))) Sort by: Most Recent

Web of Science

10 #8 AND #9 1,871
9 TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*) 5,772,934
8 #7 AND #1 7,146
7 #6 OR #5 OR #4 OR #3 OR #2 1,648,139
6 TS=(spasticity or spasm or spastic or hypertonia) 50,631
5 TS= tmj OR TS= tmjd OR TS= IBS OR TS= crohn* OR TS= colitis* OR TS= enteritis* OR TS= ileitis* 185,102
4 TS= arthrodyni* OR TS= myalgi* OR TS= myodyn* OR TS= ischialgi* OR TS= crps OR TS= brachialgia 13,911
3 TS= headache* OR TS=fibromyalgi* OR TS= causalgia OR TS= radiculopathy* OR TS= whiplash OR TS= backache* OR TS= backpain* OR TS= dorsalgi* OR TS= arthralgi* OR TS= polyarthralgi* 129,034
2 TS= pain* OR TS=osteoarthrit* OR TS= osteo-arthritis OR TS= arthrit* OR TS=neuropath* OR TS= neuralgi* OR TS=zoster* OR TS= migraine* 1,373,602
1 TS=cannabis OR TS= cannabinol OR TS= cannabinoid* OR TS=cannabidiol OR TS=bhang OR TS=hashish OR TS= hemp OR TS=marihuana OR TS= marijuana OR TS= nabilone OR TS= cesamet OR TS= tetrahydrocannabinol OR TS= dronabinol OR TS= levonantradol OR TS= nabiximols OR TS= palmidrol OR TS=tetrahydrocannabinolic OR TS=sativex OR TS= endocannabinoid* 82,113

Cannabis-Med

International Association for Cannabinoid Medicines, database of clinical studies

<http://www.cannabis-med.org/studies/study.php>

Diagnosis: Pain or spasticity

AND

Study design: Controlled Study

Cannabinoids for chronic non-cancer pain (matrix of evidence)

<https://www.epistemonikos.org/en/matrixes/58f5158d7aac87666ca8853>

97 Primary Studies

Cannabis Spasticity

45 Primary studies

eAppendix 2: Full reference list of eligible studies

(Studies reported 2 separate trials in one paper: Arai et al. 2015, and Tominaga et al 2016.)

1. Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig* 2010;30(8):489-505. doi: 10.2165/11533440-000000000-00000.
2. Andresen SR, Bing J, Hansen RM, et al. Ultramicronized palmitoylethanalamide in spinal cord injury neuropathic pain: a randomized, double-blind, placebo-controlled trial. *Pain* 2016;157(9):2097-103. doi: 10.1097/j.pain.0000000000000623 [published Online First: 2016/05/27]
3. Arai T, Kashimoto Y, Ukyo Y, Tominaga Y, Imanaka K. Two placebo-controlled, randomized withdrawal studies to evaluate the fentanyl 1 day patch in opioid-naïve patients with chronic pain. *Curr Med Res Opin* 2015;31(12):2207-18. doi: 10.1185/03007995.2015.1092127.
4. Babul N, Noveck R, Chipman H, et al. Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee. *J Pain Symptom Manage* 2004;28(1):59-71. doi: 10.1016/j.jpainsymman.2003.11.006.
5. Blake DR, Robson P, Ho M, et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)* 2006;45(1):50-2. doi: 10.1093/rheumatology/kei183 [published Online First: 2005/11/12]
6. Boureau F, Legallicier P, Kabir-Ahmadi M. Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. *Pain* 2003;104(1-2):323-31. doi: 10.1016/s0304-3959(03)00020-4.
7. Breivik H, Ljosaa TM, Stengaard-Pedersen K, et al. A 6-months, randomised, placebo-controlled evaluation of efficacy and tolerability of a low-dose 7-day buprenorphine transdermal patch in osteoarthritis patients naïve to potent opioids. *Scand J Pain* 2010;1(3):122-41. doi: 10.1016/j.sjpain.2010.05.035.
8. Burch F, Fishman R, Messina N, et al. A comparison of the analgesic efficacy of Tramadol Contramid OAD versus placebo in patients with pain due to osteoarthritis. *J Pain Symptom Manage* 2007;34(3):328-38. doi: 10.1016/j.jpainsymman.2006.11.017.
9. Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. *Expert Opin Pharmacother* 2010;11(11):1787-804. doi: 10.1517/14656566.2010.497720.
10. Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. *J Rheumatol* 1999;26(4):862-9.
11. Caldwell JR, Rapoport RJ, Davis JC, et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage* 2002;23(4):278-91. doi: 10.1016/s0885-3924(02)00383-4.
12. Christoph A, Eerdeken MH, Kok M, Volkers G, Freyhagen R. Cebranopadol, a novel first-in-class analgesic drug candidate: first experience in patients with chronic low back pain in a randomized clinical trial. *Pain* 2017;158(9):1813-24. doi: 10.1097/j.pain.0000000000000986.
13. Chu LF, D'Arcy N, Brady C, et al. Analgesic tolerance without demonstrable opioid-induced hyperalgesia: a double-blinded, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain. *Pain* 2012;153(8):1583-92. doi: 10.1016/j.pain.2012.02.028.
14. de Vries M, van Rijckevorsel DCM, Vissers KCP, et al. Tetrahydrocannabinol Does Not Reduce Pain in Patients With Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study. *Clin Gastroenterol Hepatol* 2017;15(7):1079-86 e4. doi: 10.1016/j.cgh.2016.09.147 [published Online First: 2016/10/11]
15. DeLemos BP, Xiang J, Benson C, et al. Tramadol hydrochloride extended-release once-daily in the treatment of osteoarthritis of the knee and/or hip: a double-blind, randomized, dose-ranging trial. *Am J Ther* 2011;18(3):216-26. doi: 10.1097/MJT.0b013e3181cec307.
16. Eibach L, Scheffel S, Cardebring M, et al. Cannabidiavarin for HIV-Associated Neuropathic Pain: A Randomized, Blinded, Controlled Clinical Trial. *Clin Pharmacol Ther* 2020;08:08. doi: <https://dx.doi.org/10.1002/cpt.2016>

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3 17. Fishman RL, Kistler CJ, Ellerbusch MT, et al. Efficacy and safety of 12 weeks of osteoarthritic pain therapy
4 with once-daily tramadol (Tramadol Contramid OAD). *J Opioid Manag* 2007;3(5):273-80. doi:
5 10.5055/jom.2007.0015.
- 6 18. Fleischmann RM, Caldwell JR, Roth SH, et al. Tramadol for the treatment of joint pain associated with
7 osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Current Therapeutic Research*
8 2001;62(2):113-28. doi: [https://doi.org/10.1016/S0011-393X\(01\)80021-7](https://doi.org/10.1016/S0011-393X(01)80021-7).
- 9 19. Frank B, Serpell MG, Hughes J, et al. Comparison of analgesic effects and patient tolerability of nabilone and
10 dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ*
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For peer review only

eAppendix 3: Reference list of studies excluded from quantitative analysis

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eTable 1. Psychometric studies for instruments used for measuring patient reported outcomes in eligible randomized controlled trials

Outcome	Instruments and psychometric studies
Pain relief	4-point categorical scale ¹ ; 5 point Likert scale ² ; Brief Pain Inventory ^{3,4} ; Multidimensional pain inventory (MPI-S) swedish version ⁵ ; Neuropathic Pain Scale ^{6,7} ; Short-form McGill Pain Questionnaire ³ ; Visual pain intensity scale ³ ; WOMAC Pain subscale ^{3,8}
Physical functioning	Back pain functional scale ⁹ ; Barthel index; BPI walking ability subscale ^{3,4} ; Disability Assessment Scale; Guy's Neurological Disability Scale (GNDS) ¹⁰ ; Oswestry Disability Index ^{11,12} ; Pain Disability Index ¹³ ; Roland Morris Disability Questionnaire ^{13,14} ; SF-12 PCS ¹⁵ ; Shortened Treatment Outcomes in Pain Survey instrument (S-TOPS) ¹⁶ ; WOMAC PF scale ^{3,8}
Emotional functioning	BPI mood subscale ^{3,4} ; General Health Questionnaire (GHQ-30); Profile of Mood states ³ ; VAS Bond and Lader mood ¹⁷
Role functioning	Pain Disability Index ¹³ ; S-TOPS Role-emotional disability ¹⁶
Social functioning	BPI relations with other people subscale ^{3,4} ; S-TOPS Family-social disability ¹⁶
Sleep quality	BPI sleep ^{3,4} ; Medical Outcomes Study Sleep Scale ¹⁸

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eTable 2. Baseline characteristics of eligible randomized controlled trials (N = 90 RCTs)

Author	Total # randomized	Pain condition	Age (year)	Sex (female%)	Duration of chronic pain(month)	# of arms	Interventions	Control	Length of follow-up (days)
Opioids versus placebo									
Afilalo (2010)	1030	Osteoarthritis	58	61	NR	3	Tapentadol-ER Oxycodone-ER	Placebo	84
Arai (2015)	150	Mixed neuropathic & non-neuropathic conditions	66	67	NR	2	Fentanyl-PATCH	Placebo	84
Arai (2015)	163	Mixed neuropathic	66	49	NR	2	Fentanyl-PATCH	Placebo	84
Babul (2004)	246	Osteoarthritis	61	61	154	2	Tramadol-ER	Placebo	84
Boureau (2003)	127	Postherpetic neuralgia	66	62	6.7	2	Tramadol-ER	Placebo	42
Breivik (2010)	199	Osteoarthritis	50	58	NR	2	Buprenorphine-PATCH	Placebo	180
Burch (2007)	646	Osteoarthritis	62	63	NR	2	Tramadol-ER	Placebo	84
Buynak (2010)	981	Low back pain	50	58	NR	3	Tapentadol-ER; Oxycodone-ER	Placebo	105
Caldwell (2002)	295	Osteoarthritis	61	62	NR	4	Morphine-ER	Placebo	28
Caldwell (1999)	70	Osteoarthritis	57	53	NR	3	Oxycodone-ER	Placebo	28
Christoph (2017)	252	neuropathic & non-neuropathic conditions		62	NR	5	Tapentadol-ER	Placebo	98
Chu (2012)	139	Low back pain	45	44	NR	2	Morphine-ER	Placebo	30
DeLemos (2011)	808	Osteoarthritis	60	100	96.7	2	Tramadol-ER	Placebo	84
Fishman (2007)	552	Osteoarthritis	61	62	NR	4	Tramadol-ER	Placebo	84
Fleischmann (2001)	129	Osteoarthritis	62	62	364	2	Tramadol-NR	Placebo	91
Friedmann (2011)	412	Osteoarthritis	58	70	NR	2	Oxycodone-ER	Placebo	84
Gana (2006)	1020	Osteoarthritis	58	62	NR	5	Tramadol-ER	Placebo	84
Gilron (2005)	57	Postherpetic neuralgia &painful diabetic neuropathy	50	56	NR	2	Morphine-ER	Placebo	28
Gimbel (2003)	159	Painful diabetic neuropathy			54.5	2	Oxycodone-ER	Placebo	42
Gimbel (2016)	511	Low back pain	59	48	NR	2	Buprenorphine-Buccal	Placebo	84
Gordon (2010)	78	Low back pain	54	47	NR	2	Buprenorphine-PATCH	Placebo	28
Gordon (2010)	79	Mixed neuropathic & non-neuropathic conditions	50	60	170	2	Buprenorphine-PATCH	Placebo	28

Hale (2007)	143	Low back pain	56	55	NR	2	Oxymorphone-ER	Placebo	84
Hale (2010)	268	Low back pain	48	50	NR	2	Hydromorphone-ER	Placebo	84
Hale (2015)	370	Low back pain	51	51	NR	2	Hydrocodone-ER	Placebo	84
Harati (1998)	131	Painful diabetic neuropathy	59	40	NR	2	Tramadol-NR	Placebo	42
Huse (2001)	12	Phantom limb pain	51	17	NR	2	Morphine-ER	Placebo	28
Katz (2007)	205	Low back pain	49	53	NR	2	Oxymorphone-ER	Placebo	84
Katz (2015)	389	Low back pain	49	53	NR	2	Oxycodone-ER	Placebo	84
Khoromi (2007)	55	Lumbar radiculopathy			NR	2	Morphine-ER	Placebo	49
Kawamata (2019)	130	Low back pain	53	45	NR	2	Oxycodone-ER	Placebo	49
Langford (2006)	399	Osteoarthritis	63	67	NR	2	Fentanyl-PATCH	Placebo	42
Lin (2016)	21	Low back pain	41.9	33	97.2	2	Morphine-ER	Placebo	30
Ma (2008)	116	Chronic neck pain	56	38	NR	2	Oxycodone-ER	Placebo	28
Markenson (2005)	107	Osteoarthritis	63	38	NR	2	Oxycodone-ER	Placebo	90
Matsumoto (2005)	491	Osteoarthritis	63	62	NR	4	Oxymorphone-ER Oxycodone-ER	Placebo	28
Mayorga (2016)	98	Osteoarthritis	59	56	NR	4	Oxycodone-ER	Placebo	112
Moran (1991)	15	Osteoarthritis		5	NR	2	Morphine-ER	Placebo	28
Moulin (1996)	61	Chronic post-traumatic pain	40	59	40.8	2	Morphine-ER	Placebo	77
Munera (2010)	315	Osteoarthritis	61	67	NR	2	Buprenorphine-PATCH	Placebo	28
Niesters (2014)	25	Painful diabetic neuropathy	63	41.6	NR	2	Tapentadol-ER	Placebo	28
Norrbrink (2009)	36	Post-traumatic neuralgia	51	78	NR	2	Tramadol-NR	Placebo	28
Peloso (2000)	103	Osteoarthritis	62	40	NR	2	Codeine-ER	Placebo	28
Raja (2002)	76	Postherpetic neuralgia			NR	2	Morphine-ER	Placebo	56
Rauck (2013)	990	Osteoarthritis	50	56	NR	3	Hydromorphone-ER	Placebo	84
Rauck (2014)	302	Low back pain	50	63	NR	2	Hydrocodone-ER	Placebo	84
Rauck (2016)	420	Low back pain	59	64	NR	2	Buprenorphine-Buccal	Placebo	84
Russell (2000)	69	Fibromyalgia	49	94	NR	2	Tramadol-ER	Placebo	42
Schnitzer (2000)	254	Low back pain	47	50	NR	2	Tramadol-NR	Placebo	28
Schwartz (2011)	395	Painful diabetic neuropathy	62	43	76	2	Tapentadol-ER	Placebo	84

1	Serrie (2017)	990	Osteoarthritis	62	69	NR	3	Tapentadol-ER Oxycodone-ER	Placebo	105
2	Simpson (2016)	186	Diabetic neuropathy	63	33	NR	2	Buprenorphine-PATCH	Placebo	84
3	Sindrup (1999)		Painful diabetic neuropathy	57	24	36		Tramadol-ER	Placebo	28
4	Sindrup (2012)	64	Painful polyneuropathy			NR	3	Tramadol-ER	Placebo	28
5	Steiner (2011)	541	Low back pain	49	55	108.6	2	Buprenorphine-PATCH	Placebo	84
6	Thorne (2008)	100	Osteoarthritis	61	55	NR	2	Tramadol-ER	Placebo	28
7	Tominaga (2016)	91	neuropathic & non-neuropathic conditions			NR	2	Tapentadol-ER	Placebo	84
8	Tominaga (2016)	91	Postherpetic neuralgia & painful diabetic neuropathy			NR	2	Tapentadol-ER	Placebo	84
9	Uberall (2012)	240	Low back pain			NR	2	Tramadol-ER	Placebo	28
10	Vinik (2014)	320	Painful diabetic neuropathy	58	41	NR	2	Tapentadol-ER	Placebo	84
11	Vojtassak (2011)	288	Osteoarthritis	66	72	NR	2	Hydromorphone-ER	Placebo	112
12	Vorsanger (2008)	386	Low back pain	47	50	NR	3	Tramadol-ER	Placebo	84
13	Watson (1998)	50	Postherpetic neuralgia	70	44	31	2	Oxycodone-ER	placebo	28
14	Webster (2006)	307	Low back pain	48	61	NR	4	Oxycodone-ER	Placebo	84
15	Wen (2015)	588	Low back pain	48	57	NR	2	Hydrocodone	Placebo	84
16	Wu (2008)	60	postamputation	63	21	51.3	2	Morphine-ER	Placebo	42
17	Opioids versus cannabis for medical use									
18	Frank 2008	192	Neuropathic pain	50	26	76.4	2	THC, Nabilone	Dihydrocodeine	42
19	Cannabis for medical use versus placebo									
20	Andresen (2016)	73	Spinal cord injury-related neuropathic pain	56	26	≥3	2	PEA	Placebo	84
21	Blake (2006)	58	Rheumatoid arthritis pain	63	79	NR	2	THC/CBD, Nabiximols	Placebo	48
22	de Vries (2017)	65	Chronic abdominal pain	53	39	≥3	2	THC, Namisol	Placebo	51
23	Eibach (2020)	68	HIV associated neuropathic pain	50	6	157.2	2	Cannabidiol (CBDV)	Placebo	28
24	Germini (2017)	20	Mixed chronic noncancer pain	83	100	≥6	2	PEA	Placebo	42
25	Hunter (2018)	320	Osteoarthritis	62	51	≥12	2	CBD synthetic gel	Placebo	84
26	Langford (2013)	339	Multiple sclerosis central pain	49	68	65.5	2	THC/CBD, Nabiximols	Placebo	98
27	Markova (2018)	106	Multiple sclerosis with pain (no details)	51.3	80	170.4	2	THC/CBD, Nabiximols	Placebo	84

		(about pain condition)						
NCT00710424 (2006)	297	Diabetic neuropathy	60	38	≥6	2	THC/CBD, Nabiximols	Placebo
Novotna (2011)	241	Multiple sclerosis with pain (no details about pain condition)	49	60	151.2	2	THC/CBD, Nabiximols	Placebo
Nurmikko (2007)	125	Peripheral neuropathic pain	53	59	75.6	2	THC/CBD, Nabiximols	Placebo
Pinsger (2006)	60	Refractory pain related to musculoskeletal system	55	77	240	2	THC, Nabilone	Placebo
Rog (2005)	66	Multiple sclerosis central pain	49	79	138.8	2	THC/CBD	Placebo
Schimrigk (2017)	240	Multiple sclerosis central pain	48	73	NR	2	THC, Marinol	Placebo
Selvarajah (2010)	30	Diabetic neuropathy	56	37	NR	2	THC/CBD, Nabiximols	Placebo
Serpell (2014)	246	Peripheral neuropathy	57	61	75.6	2	THC/CBD, Nabiximols	Placebo
Skrabek (2008)	40	Fibromyalgia	49	NR	NR	2	THC, Nabilone	Placebo
Toth (2012)	26	Diabetic neuropathy	61	46	85.8	2	THC, Nabilone	Placebo
van Amerongen (2018)	24	Multiple sclerosis neuropathic pain and spasticity	54	6	137.4	2	THC, Namisol	Placebo
Wissel (2006)	26	Chronic upper motor neuron syndrome	44.8	69	NR	2	THC, Nabilone	Placebo
Xu (2020)	29	Peripheral neuropathic pain	68	38	≥3	2	CBD	Placebo
Zajicek (2003 and 2005)	657	Multiple sclerosis with pain (no details about pain condition)	51	63	NR	2	THC/CBD, Marinol	Placebo
Zajicek (2012)	279	Multiple sclerosis with pain (no details about pain condition)	52	63	NR	2	THC/CBD	Placebo

eTable 3. Risk of bias assessment of the eligible randomized controlled trials (N = 90 RCTs)

Study	Loss to follow-up (%)	Randomization	Concealment	Blinding of patients	Blinding of care providers	Blinding of data collectors	Blinding of outcome assessors
Afilalo 2010	51	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Andresen 2016	15	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Arai 2015a	49	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Arai 2015b	54	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Babul 2004	50	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Blake 2006	7	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Boureau 2003	15	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Breivik 2010	44	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Burch 2007	24	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Buynak 2010	53	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Caldwell 1999	34	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Caldwell 2002	38	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Christoph 2017	30	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Chu 2012	26	inadequate randomization	inadequate allocation concealment	Yes	No	Yes	Yes
de Vries 2017	25	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
DeLemos 2011	48	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Eibach 2020	18	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Fishman 2007	44	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Fleischmann 2001	71	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Frank 2008	24	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Friedmann 2011	36	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Gana 2006	45	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes

1	Germini 2017	30	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes
2	Gilron 2005	9	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes
3	Gimbel 2003	28	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
4	Gimbel 2016	31	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes
5	Gordon 2010a	35	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes
6	Gordon 2010b	37	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
7	Hale 2007	53	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes
8	Hale 2010	59	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
9	Hale 2015	20	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
10	Harati 1998	37	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
11	Hunter 2018	26	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes
12	Huse 2001	17	inadequate randomization	inadequate allocation concealment	No	No	No
13	Katz 2007	42	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes
14	Katz 2015	43	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
15	Kawamata 2019	37	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes
16	Khoromi 2007	33	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes
17	Langford 2006	52	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
18	Langford 2013	12	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes
19	Lin 2016	0	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes
20	Ma 2008	90	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes
21	Markenson 2005	66	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
22	Markova 2018	9	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes
23	Matsumoto 2005	45	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
24	Mayorga 2016	61	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
25	Moran 1991	25	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes

Moulin 1996	25	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Munera 2010	51	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
NCT00710424 2006	23	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Niesters 2014	0	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Norrbrink 2009	36	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Novotna 2011	7	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Nurmikko 2007	16	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Peloso 2000	36	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Pinsger 2006	30	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Raja 2002	42	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Rauck 2013	51	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	No
Rauck 2014	39	inadequate randomization	adequate allocation concealment	Yes	Yes	No	No
Rauck 2016	9	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Rog 2005	3	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Russell 2000	1	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Schimrigk 2017	26	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Schnitzer 2000	43	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Schwartz 2011	33	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Selvarajah 2010	20	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Serpell 2014	30	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Serrie 2017	46	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Simpson 2016	33	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Sindrup 1999	20	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Sindrup 2012	8	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Skrabek 2008	18	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes

Steiner 2011	32	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Thorne 2008	25	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Tominaga 2016a	13	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Tominaga 2016b	9	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Toth 2012	4	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Uberall 2012	25	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
van Amerongen 2018	4	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Vinik 2014	29	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Vojtassak 2011	31	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Vorsanger 2008	38	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Watson 1998	22	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Webster 2006	54	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Wen 2015	25	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Wissel 2006	15	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Wu 2008	41	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Xu 2020	21	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Zajicek 2003 & 2005	4	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Zajicek 2012	20	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes

eTable 4. Network estimates and their certainty in evidence (GRADE) evaluating the effects of opioid and cannabis for medical use therapy in patients with chronic non-cancer pain across different outcomes

Outcome	Comparison	Direct Estimate MD (95% CI)	Indirect Estimate MD (95% CI)	Network Estimate* MD (95% CrI))	GRADE
Pain (VAS 0-10)	Opioid vs placebo	<u>-0.84 (-0.99, -0.69)</u>	<u>-0.83 (-0.97, -0.70)</u>	<u>-0.83 (-0.97, -0.70)</u>	Moderate ²
	Cannabis for medical use vs placebo	<u>-0.63 (-0.94, -0.32)</u>	<u>-0.59 (-0.88, -0.32)</u>	<u>-0.60 (-0.87, -0.33)</u>	Low ^{2,8}
	Cannabis for medical use vs opioid	0.13 (-0.54, 0.80)	0.24 (-0.07, 0.55)	0.23 (-0.06, 0.53)	Low ^{1,8}
Physical function (SF 0-100)	Opioid vs placebo	<u>2.38 (1.05, 3.72)</u>	—	<u>2.05 (1.01, 3.29)</u>	Moderate ⁸
	Cannabis for medical use vs placebo	<u>3.00 (0.08, 5.91)</u>	—	<u>2.52 (0.37, 4.91)</u>	Moderate ⁸
	Cannabis for medical use vs opioid	—	0.47 (-1.97, 2.99)	0.47 (-1.97, 2.99)	Moderate ²
Emotional function (SF 0-100)	Opioid vs placebo	-0.00 (-1.09, 1.09)	—	-0.15 (-1.10, 0.92)	High
	Cannabis for medical use vs placebo	0.72 (-1.01, 2.45)	—	0.70 (-1.42, 2.84)	Moderate ⁸
	Cannabis for medical use vs opioid	—	0.85 (-1.55, 3.18)	0.85 (-1.55, 3.18)	Low ^{2,8}
Role function (SF 0-100)	Opioid vs placebo	0.91 (-1.17, 2.98)	—	0.94 (-1.26, 3.17)	Moderate ⁸
	Cannabis for medical use vs placebo	1.27 (-12.39, 14.93)	—	0.88 (-3.78, 6.05)	Moderate ⁸
	Cannabis for medical use vs opioid	—	-0.05 (-5.16, 5.60)	-0.05 (-5.16, 5.60)	Moderate ⁸
Social function (SF 0-100)	Opioid vs placebo	0.47 (-1.47, 2.41)	—	1.17 (-1.72, 4.58)	Moderate ⁸
	Cannabis for medical use vs placebo	-1.82 (-5.79, 2.15)	—	1.70 (-3.28, 8.13)	Moderate ⁸
	Cannabis for medical use vs opioid	—	0.55 (-5.34, 7.41)	0.55 (-5.34, 7.41)	Moderate ⁸
Sleep quality (0-100)	Opioid vs placebo	<u>5.55 (2.67, 8.43)</u>	—	<u>5.46 (2.62, 8.59)</u>	Moderate ²
	Cannabis for medical use vs placebo	<u>6.04 (1.43, 10.66)</u>	—	<u>5.95 (1.82, 10.24)</u>	Low ^{2,8}
	Cannabis for medical use vs opioid	—	0.49 (-4.72, 5.59)	0.49 (-4.72, 5.59)	Low ^{2,8}
Outcome	Comparison	Direct Estimate OR (95% CI)	Indirect Estimate OR (95% CI)	Network Estimate* OR (95% CrI)	GRADE
Discontinuations due to adverse events (enriched)	Opioid vs placebo	<u>1.39 (1.04, 1.86)</u>	-	1.25 (0.91, 1.67)	Low ^{1,8}
	Cannabis for medical use vs placebo	5.00 (0.25, 101.7)	-	0.96 (0.09, 10.80)	Low ^{1,8}
	Cannabis for medical use vs opioid		0.77 (0.07, 8.83)	0.77 (0.07, 8.83)	Low ^{1,8}
Discontinuations due to adverse events (non-enriched)	Opioid vs placebo	<u>3.58 (3.00, 4.27)</u>	<u>3.27 (2.70, 3.93)</u>	<u>3.27 (2.71, 3.90)</u>	Moderate ¹
	Cannabis for medical use vs placebo	<u>2.47 (1.49, 4.11)</u>	<u>1.78 (1.15, 2.63)</u>	<u>1.80 (1.19, 2.63)</u>	High
	Cannabis for medical use vs opioid	0.50 (0.16, 1.61)	<u>0.54 (0.34, 0.84)</u>	<u>0.55 (0.36, 0.83)</u>	Moderate ¹

* Imprecision only incorporated at network level not at direct or indirect.

Abbreviations: MD: Mean difference; 95 CI%: 95% Confidence Intervals; GRADE Certainty of Evidence.

GRADE Assessment: Reasons for downgrading direct evidence:

1. Rated down due to risk of bias
2. Rated down due to inconsistency
3. Rated down due to imprecision (effects were rated down if the associated measure of precision included no effect [a mean difference of 0])
4. Rated down due to indirectness
5. Rated down due to publication bias

Reasons for downgrading indirect evidence:

6. Rated down for intransitivity

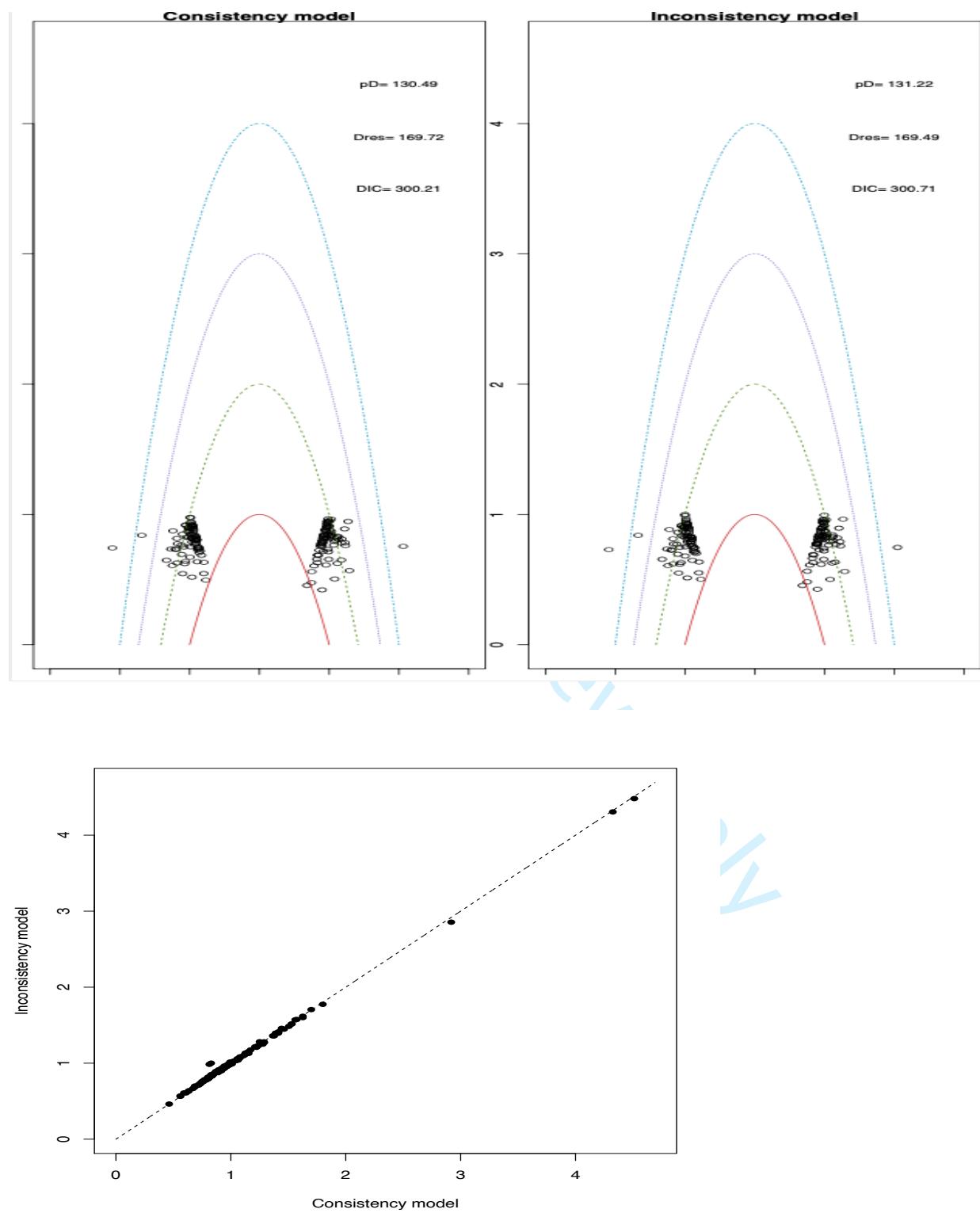
Reasons for downgrading network evidence

7. Rated down due to incoherence

8. Rated down due to imprecision (either due to inclusion of the null value in the 95%CI, or because the evidence is provided by a small number of patients – a total number of patients less than the optimal information size [n=300])

When two of the same superscripts are listed with an estimate of treatment effect (e.g. ^{1,1}), this means the certainty of evidence (GRADE) was downgraded for 2 levels (-2), instead of one (-1)

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eFigure 1. Pain, random effects consistency and inconsistency model

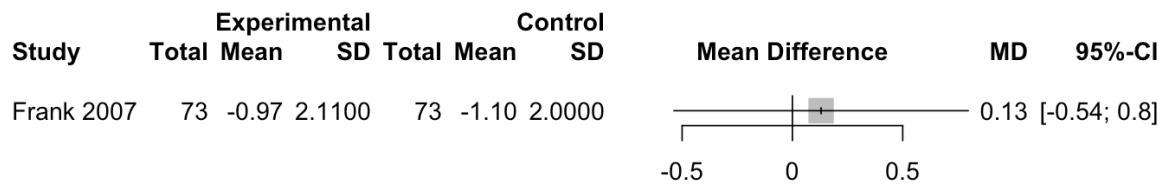


eTable 5. Pain, node splitting outputs

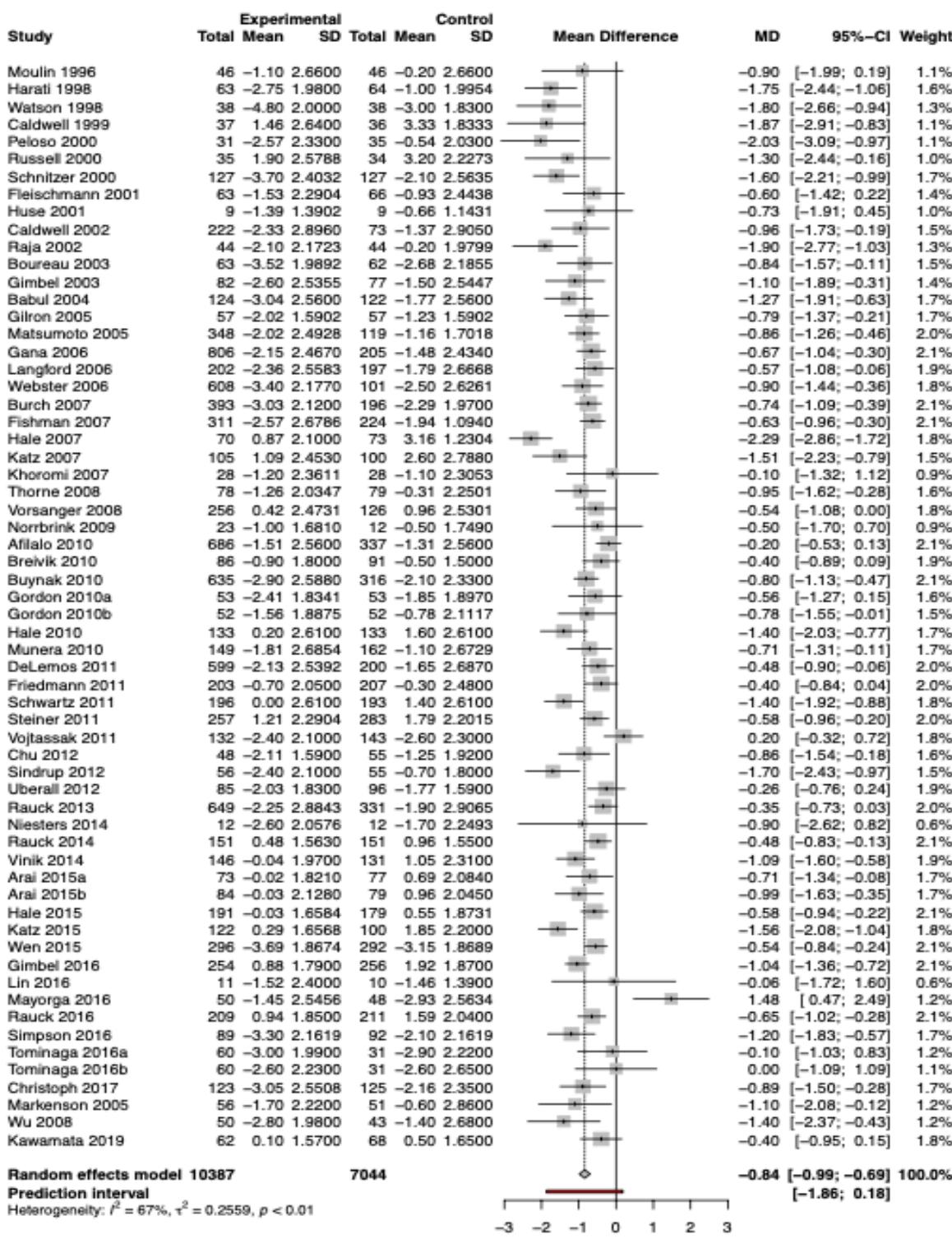
Comparison of direct versus indirect evidence - Mean change in pain VAS from baseline

Comparisons	Direct evidence	Indirect evidence
Cannabis for medical use vs. Opioids	0.13 (-0.54, 0.80)	0.23 (-0.10, 0.55)

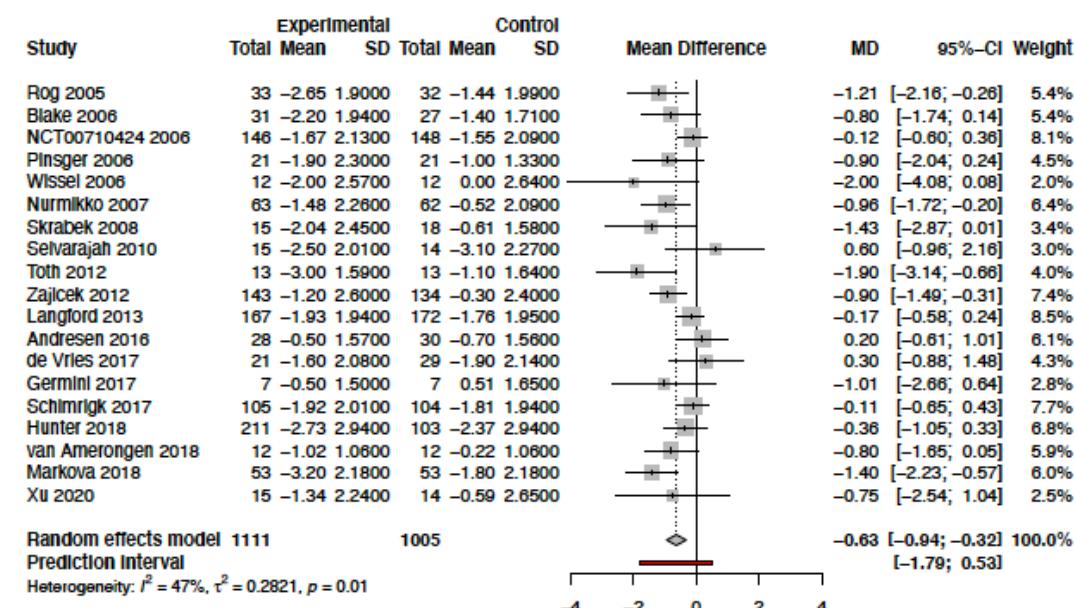
P-value = 0.792

Direct evidence forest plot

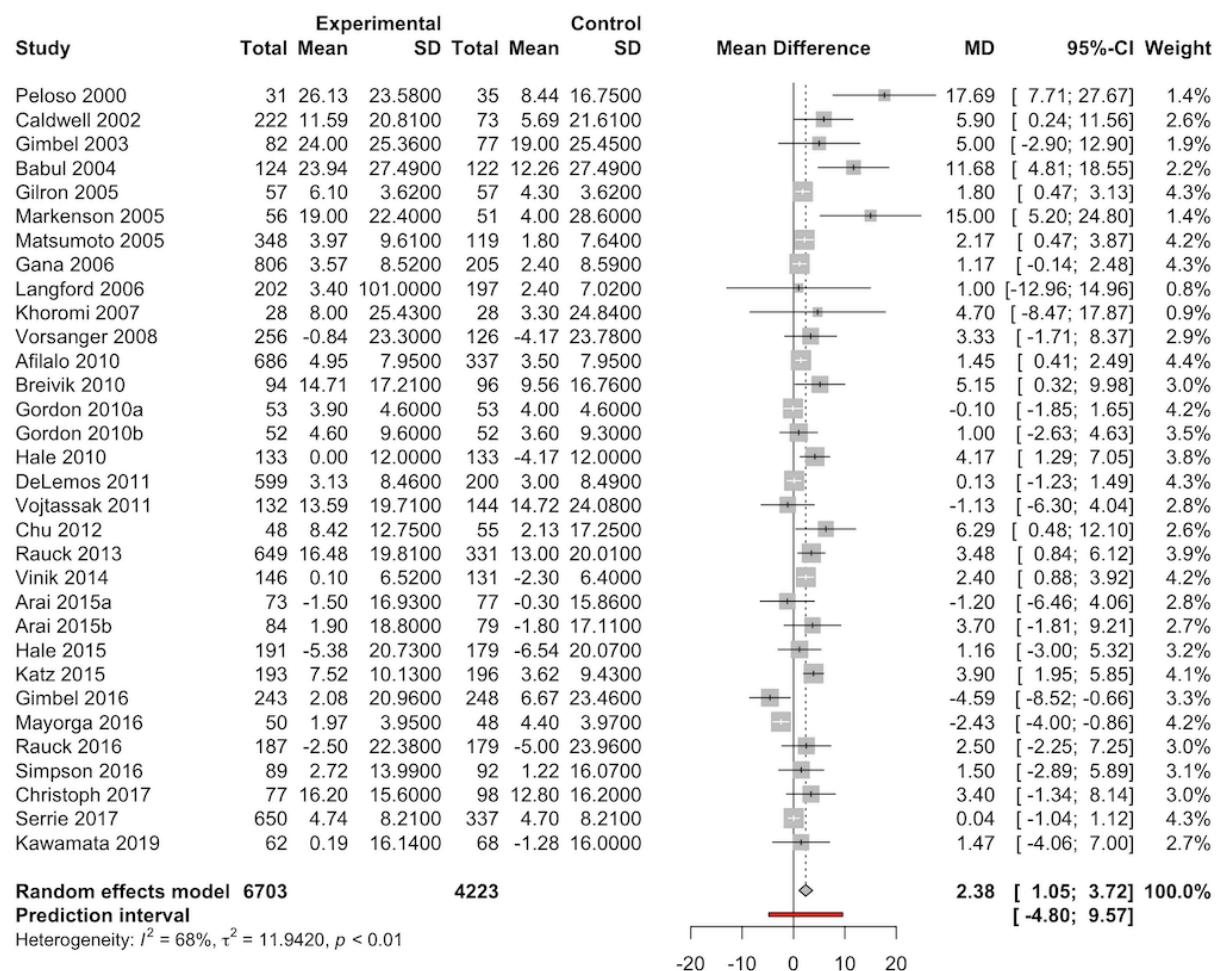
eFigure 2. Pain, opioids versus placebo pairwise meta-analysis random effect model



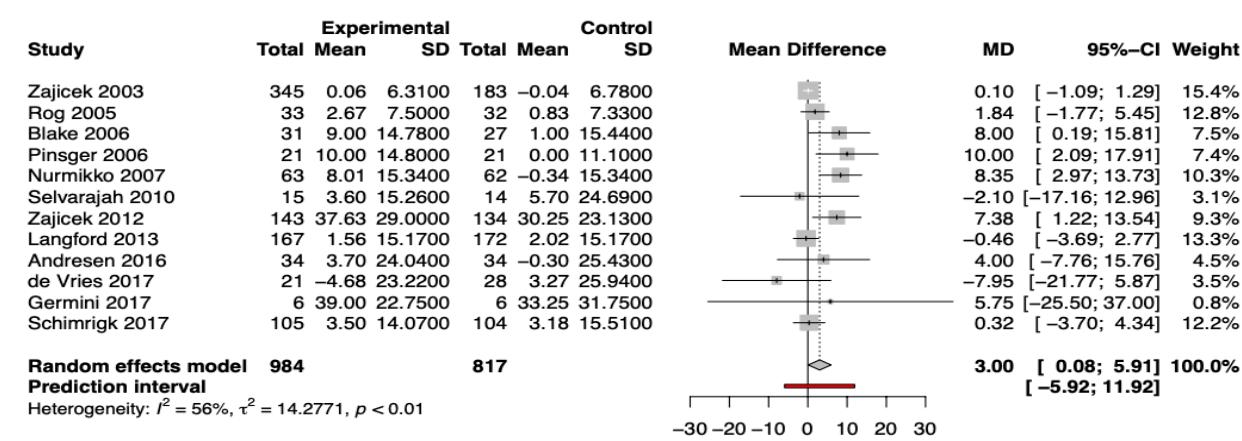
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5 eFigure 3. Pain, cannabis for medical use versus placebo pairwise meta-analysis random effects model
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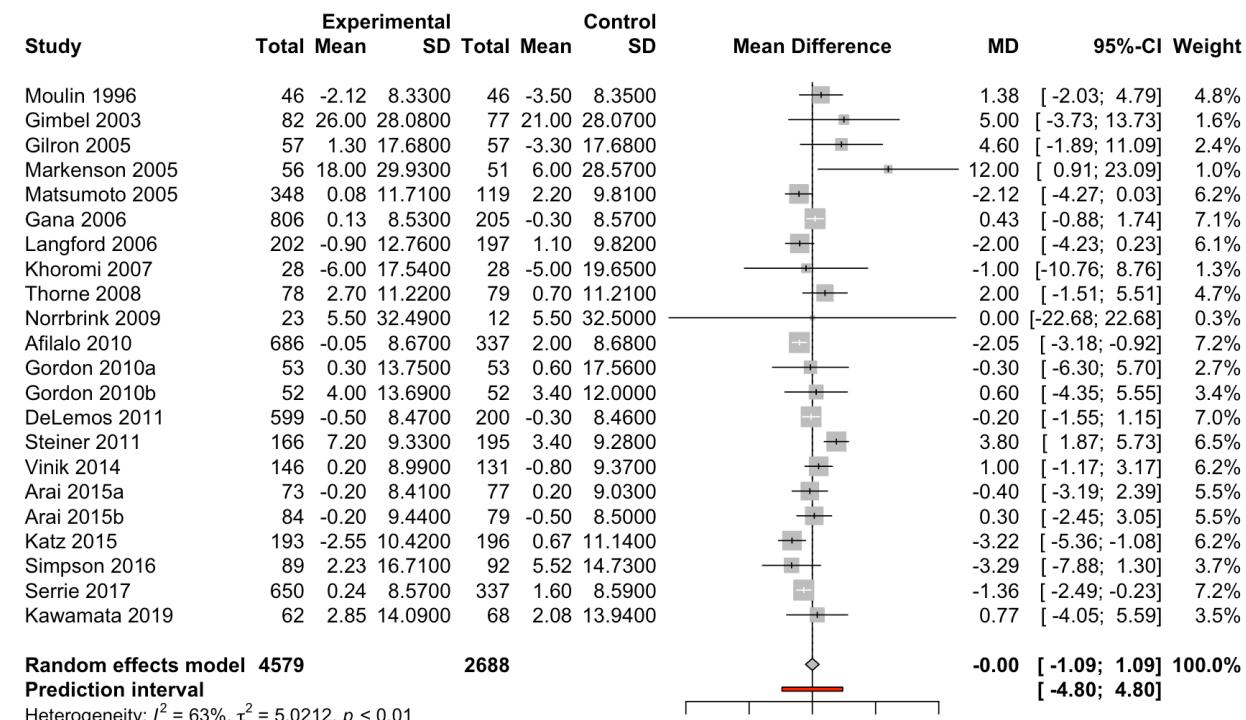
eFigure 4. Physical functioning, opioids versus placebo pairwise meta-analysis random effect model



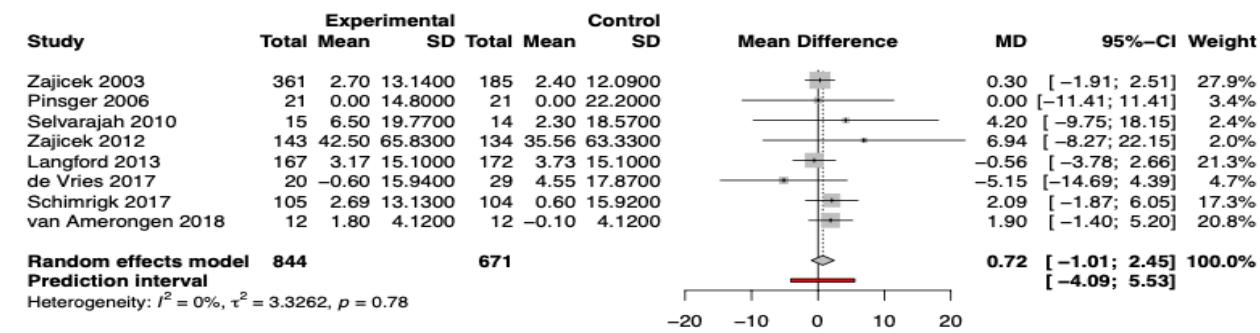
eFigure 5. Physical functioning, cannabis for medical use versus placebo pairwise meta-analysis random effect model



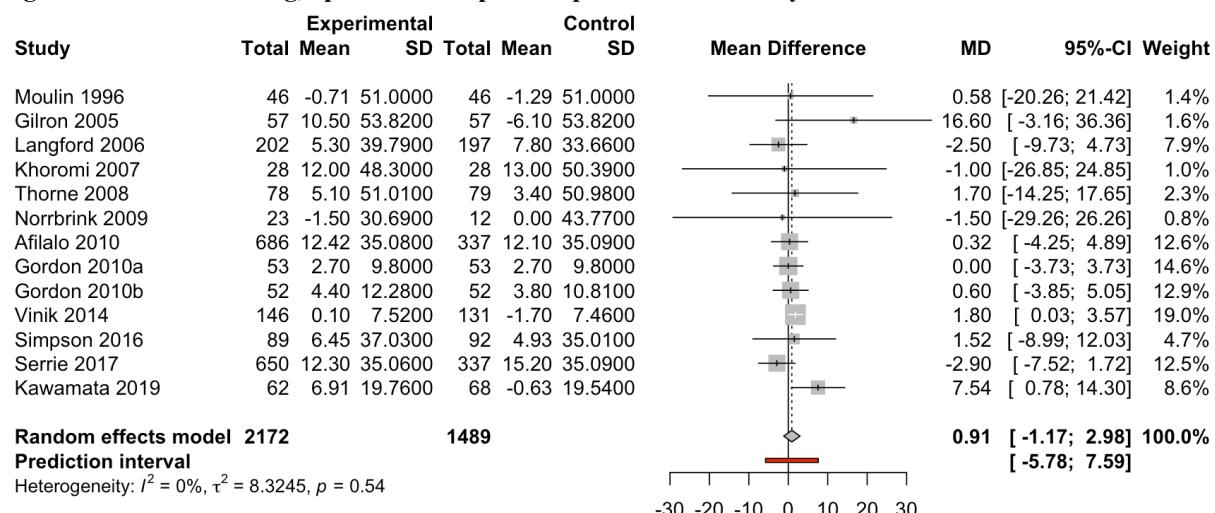
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5 eFigure 6. Emotional functioning, opioids versus placebo pairwise meta-analysis random effect model
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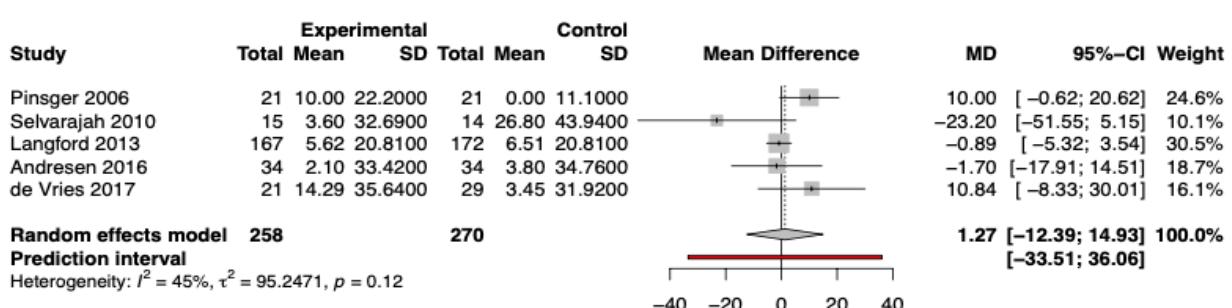
31 eFigure 7. Emotional functioning, cannabis for medical use versus placebo pairwise meta-analysis random
32 effect model
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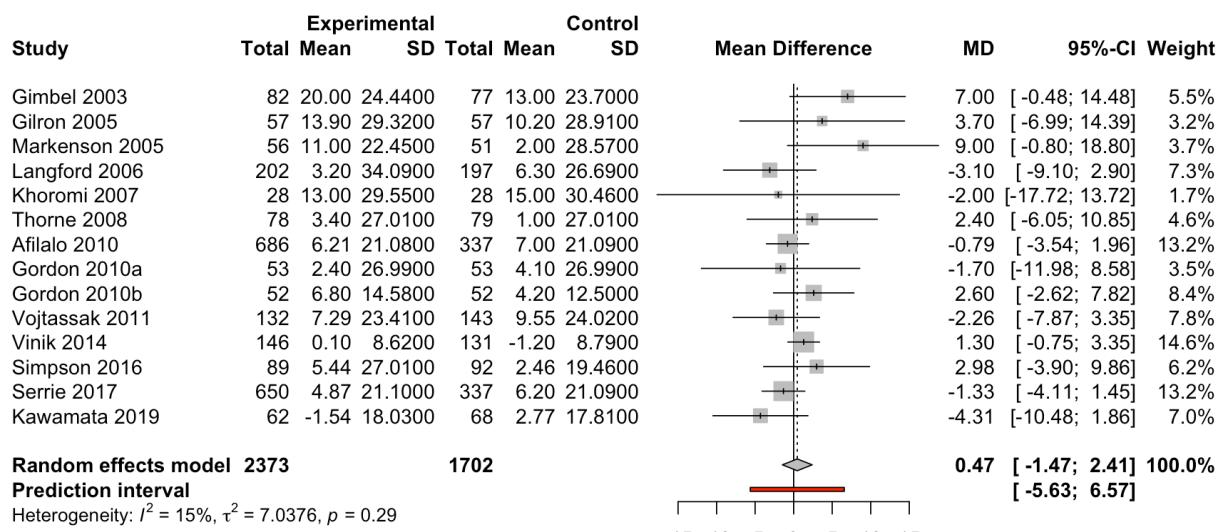
eFigure 8. Role functioning, opioids versus placebo pairwise meta-analysis random effect model



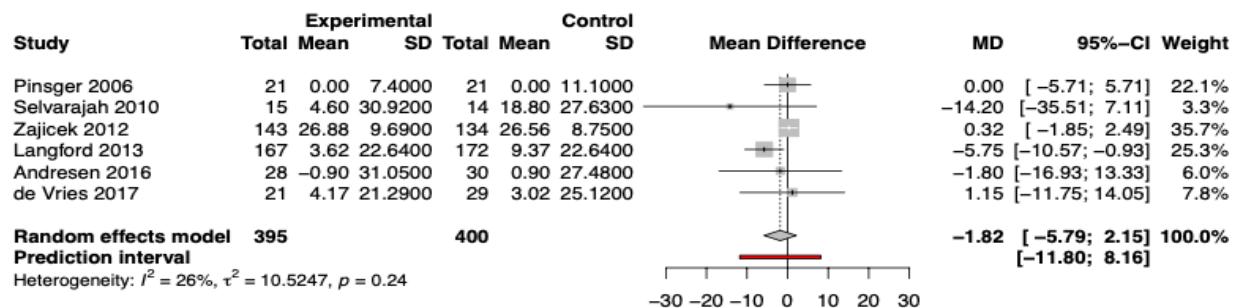
eFigure 9. Role functioning, cannabis for medical use versus placebo pairwise meta-analysis random effect model



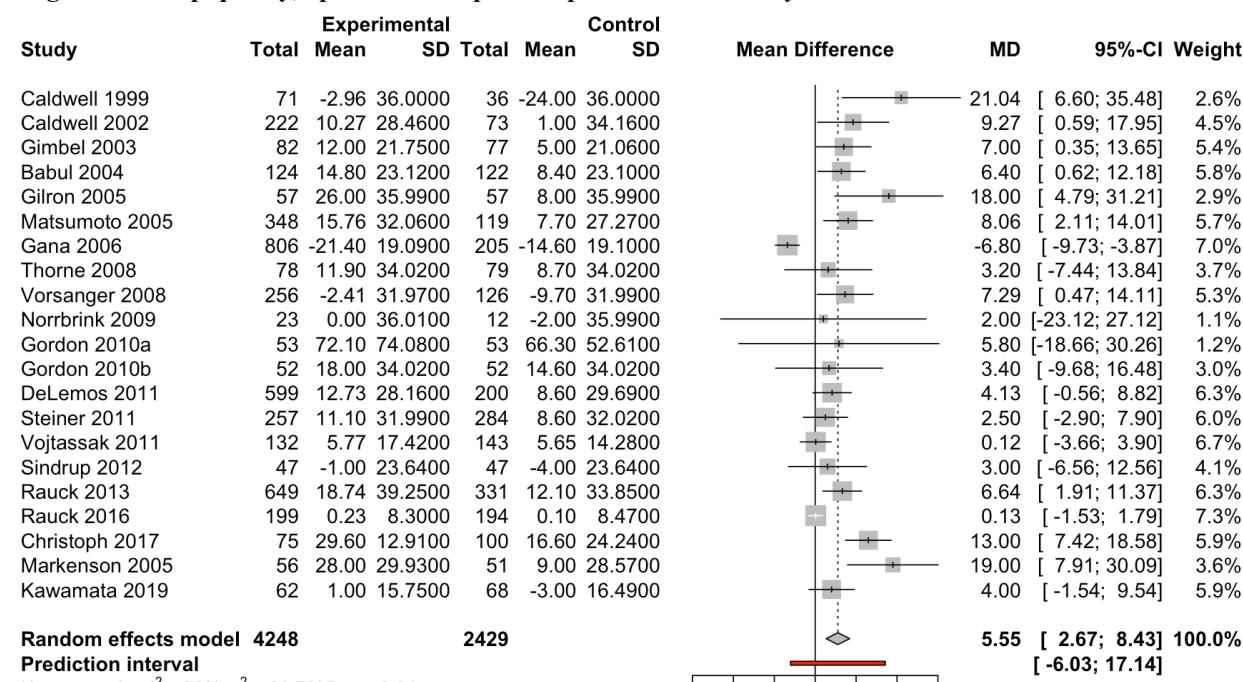
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5 eFigure 10. Social functioning, opioids versus placebo pairwise meta-analysis random effect model
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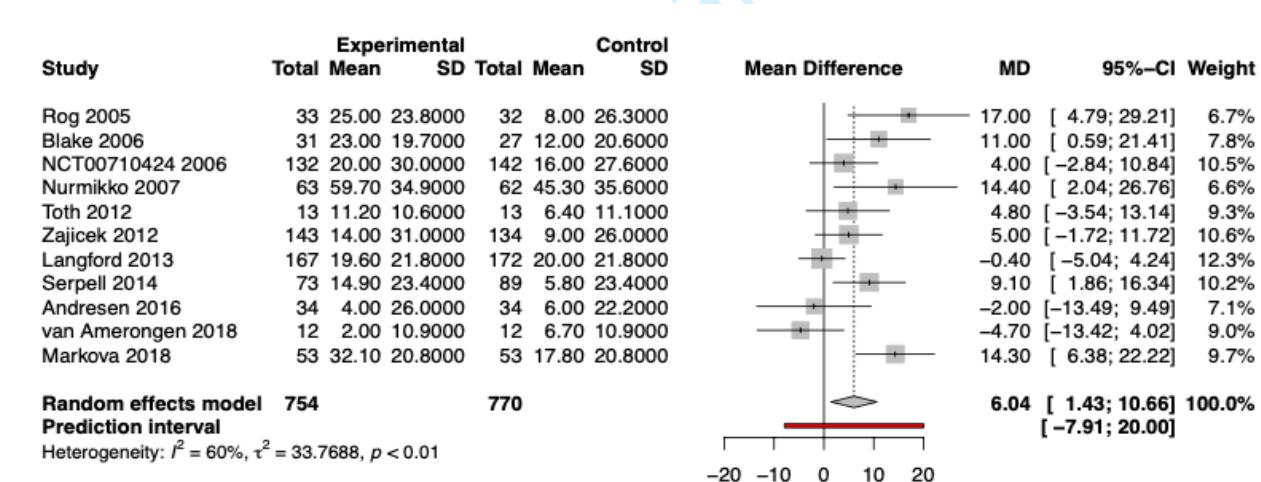
24
25 eFigure 11. Social functioning, cannabis for medical use versus placebo pairwise meta-analysis random effect
26 model
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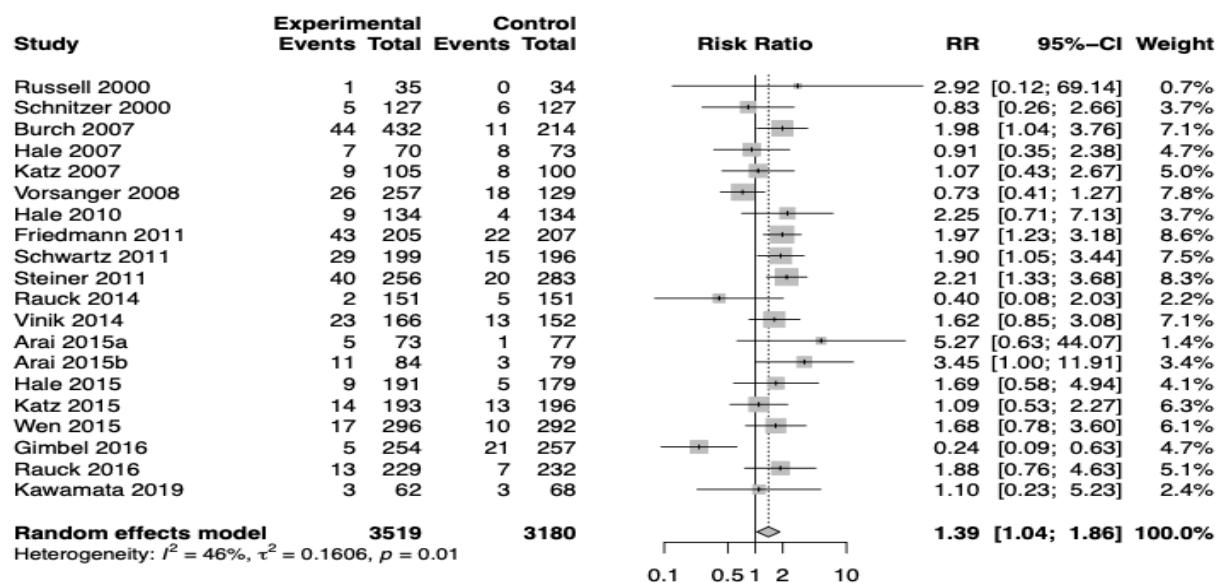
eFigure 12. Sleep quality, opioids versus placebo pairwise meta-analysis random effect model



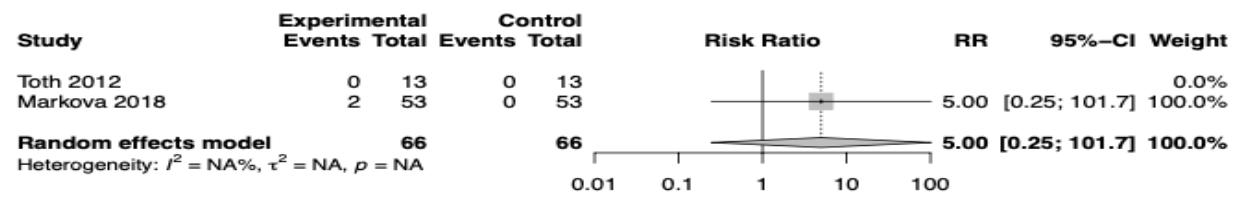
eFigure 13. Sleep quality, cannabis for medical use versus placebo pairwise meta-analysis random effect model



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5 eFigure 14. Discontinuations due to adverse events (enriched trials), opioids versus placebo pairwise meta-analysis random effect model
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28 eFigure 15. Discontinuations due to adverse events (enriched trials), cannabis for medical use versus placebo
29 pairwise meta-analysis random effect model
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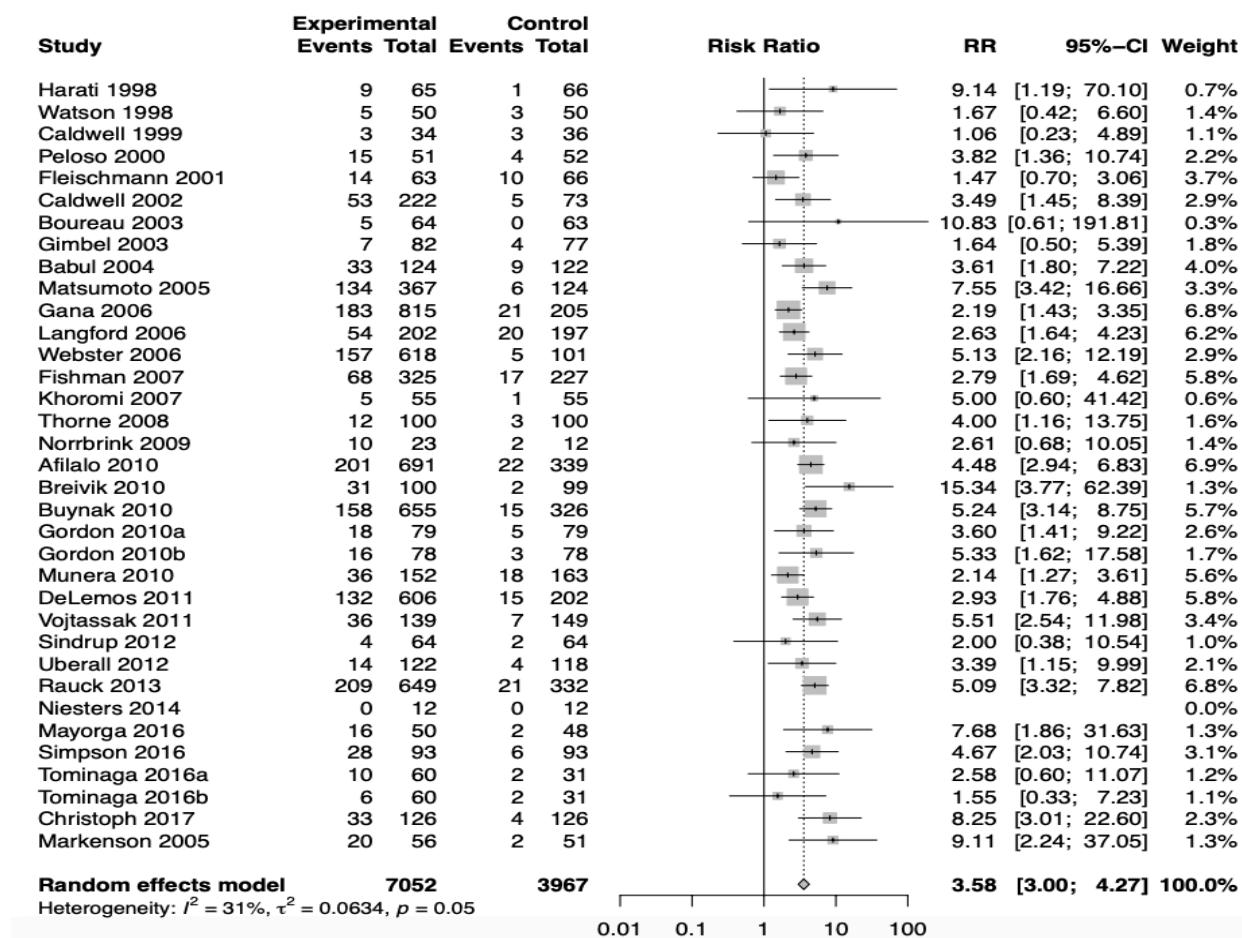
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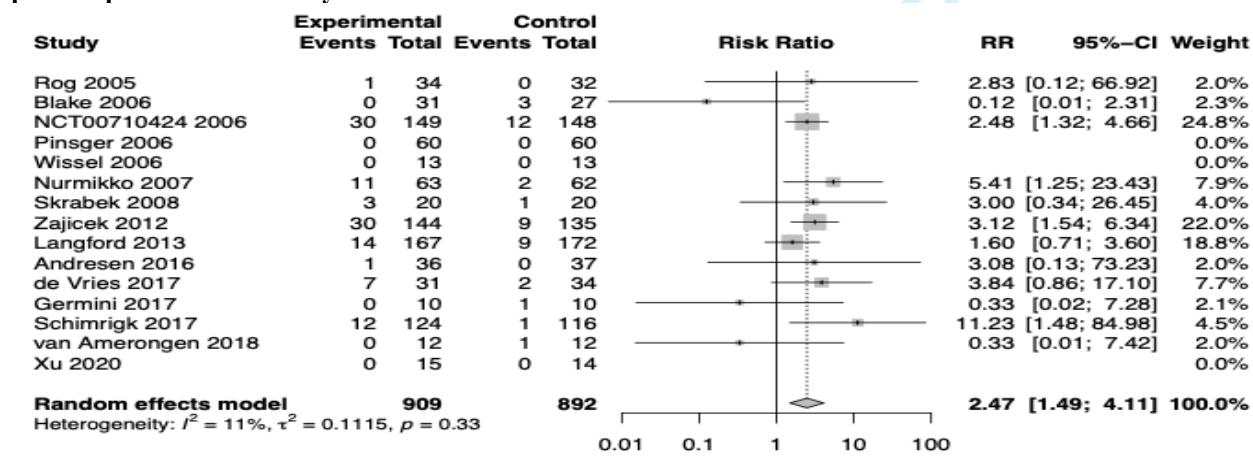
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eFigure 16. Discontinuations due to adverse events (non-enriched trials), opioids versus placebo pairwise meta-analysis random effect model



eFigure 17. Discontinuations due to adverse events (non-enriched trials), cannabis for medical use versus placebo pairwise meta-analysis random effect model



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5 **eAppendix 4: Reference list of cannabis for medical use studies with incomplete EQ-5D and SF-36 general**
6 **health data**

7 **EQ-5D:**

- 8 1. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel- group study
9 of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central
10 neuropathic pain in patients with multiple sclerosis. *J Neurol* 2013;260(4):984-97. doi: 10.1007/s00415-012-
11 6739-4 [published Online First: 2012/11/28]
12 2. Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel- group,
13 enriched-design study of nabiximols* (Sativex((R))), as add-on therapy, in subjects with refractory spasticity
14 caused by multiple sclerosis. *Eur J Neurol* 2011;18(9):1122-31. doi: 10.1111/j.1468-1331.2010.03328.x
15 [published Online First: 2011/03/03]
16 3. NCT00710424. A Study of Sativex® for Pain Relief Due to Diabetic Neuropathy:
17 <https://ClinicalTrials.gov/show/NCT00710424>, 2006.
18 4. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of
19 cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding
20 factor. *Diabetes Care* 2010;33(1):128-30. doi: 10.2337/dc09-1029 [published Online First: 2009/10/08]
21 5. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind,
22 placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic
23 peripheral neuropathic pain. *Pain* 2012;153(10):2073-82. doi: 10.1016/j.pain.2012.06.024 [published Online
24 First: 2012/08/28]

25 **SF-36 General health:**

- 26 1. Frank B, Serpell MG, Hughes J, et al. Comparison of analgesic effects and patient tolerability of nabilone and
27 dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ*
28 2008;336(7637):199-201. doi: 10.1136/bmj.39429.619653.80 [published Online First: 2008/01/10]
29 2. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel- group study
30 of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central
31 neuropathic pain in patients with multiple sclerosis. *J Neurol* 2013;260(4):984-97. doi: 10.1007/s00415-012-
32 6739-4 [published Online First: 2012/11/28]
33 3. Markova J, Essner U, Akmaz B, et al. Sativex((R)) as add-on therapy vs. further optimized first-line
34 ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled
35 randomised clinical trial. *Int J Neurosci* 2019;129(2):119-28. doi: 10.1080/00207454.2018.1481066 [published
36 Online First: 2018/05/25]
37 4. Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel- group,
38 enriched-design study of nabiximols* (Sativex((R))), as add-on therapy, in subjects with refractory spasticity
39 caused by multiple sclerosis. *Eur J Neurol* 2011;18(9):1122-31. doi: 10.1111/j.1468-1331.2010.03328.x
40 [published Online First: 2011/03/03]
41 5. NCT00710424. A Study of Sativex® for Pain Relief Due to Diabetic Neuropathy:
42 <https://ClinicalTrials.gov/show/NCT00710424>, 2006.
43 6. Schimrigk S, Marziniak M, Neubauer C, et al. Dronabinol Is a Safe Long-Term Treatment Option for
44 Neuropathic Pain Patients. *European neurology* 2017;78(5-6):320-29. doi: 10.1159/000481089 [published
45 Online First: 2017/10/27]
46 7. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of
47 cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding
48 factor. *Diabetes Care* 2010;33(1):128-30. doi: 10.2337/dc09-1029 [published Online First: 2009/10/08]

eTable 6. ICEMAN criteria for assessing the credibility of subgroup effects

Criteria	Subgroup effects of neuropathic vs non-neuropathic pain for outcomes below		
	Pain	Social function	Discontinuation due to adverse events (non-enriched)
1: Is the analysis of effect modification based on comparison within rather than between trials?	Between-study	Between-study	Between-study
2: For within-trial comparisons, is the effect modification similar from trial to trial?	Not applicable	Not applicable	Not applicable
3: For between-trial comparisons, is the number of trials large?	Large (55 studies with non-neuropathic pain; 26 studies with neuropathic pain)	Large (11 studies with non-neuropathic pain; 8 study with neuropathic pain)	Large (33 studies with non-neuropathic pain; 17 studies with neuropathic pain)
4: Was the direction of effect modification correctly hypothesized a priori?	Probably no (opposite)	Probably no (opposite)	Probably no (opposite)
5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification?	Chance an unlikely explanation ($p=0.004$)	Chance a likely explanation ($p=0.047$)	Chance a very likely explanation ($p=0.052$)
6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?	Probably no (5 factors)	Probably no (5 factors)	Probably no (5 factors)
7: Did the authors use a random effects model?	Definitely yes	Definitely yes	Definitely yes
8: If the effect modifier is a continuous variable, were arbitrary cut points avoided?	NA	NA	NA
9 Optional: Are there any additional considerations that may increase or decrease credibility?			
The effect modification persisted after adjustment for other potential effect modifiers	NA	NA	NA
The effect modification is consistent across related outcomes	Yes	Yes	Yes
A sensitivity analysis suggested robustness to relevant assumptions	NA	NA	NA
Effect modification supported by external evidence	NA	NA	NA
“Dose-response effect” across levels of the effect modifier	NA	NA	NA
Risk of bias of the main effects of the individual RCTs or the meta-analysis	NA	NA	NA
The meta-analysis had had exceptionally high power to detect the effect modification	NA	NA	NA
Overall credibility	Low	Very low	Very low

eTable 7. Subgroup analysis for pain and secondary outcomes with moderate to high certainty evidence

Subgroup factors		Pain relief			Physical functioning			Role functioning			Social functioning			Discontinuations due to adverse events (non-enriched)			
		No studies	WMD 95% CrI	p-value	No studies	WMD 95% CrI	p-value	No studies	WMD 95% CrI	p-value	No studies	WMD 95% CrI	p-value	No studies	OR 95% CrI	p-value	
Clinical condition	Neuropathic	26	0.74 (0.30,1.12)	0.004	11	-0.67 (-4.46, 3.28)	0.55	8	-4.66 (-21.16,5.49)	0.10	8	-8.09 (-16.89,-0.69)	0.047	17	0.91 (0.48, 1.76)	0.052	
	Non-neuropathic	55	-0.12 (-0.55,0.30)		32	0.97 (-2.67, 4.72)		9	9.81 (-1.55,21.10)		11	1.01 (-3.01,4.75)		33	*0.34* (0.15, 0.67)		
Length of follow-u	≤ 2 months	39	0.04 (-0.36,0.45)	0.228	17	2.35 (-2.72,6.56)	0.59	10	8.59 (-3.64,20.37)	0.14	10	-0.31 (-8.27,7.79)	0.70	29	*0.42* (0.20, 0.79)	0.338	
	>2 months	43	0.41 (-0.04,0.85)		27	-0.75 (-3.83, 2.38)		8	-2.48 (-11.89, 5.23)		10	-2.26 (-9.50,2.29)		22	0.65 (0.37, 1.16)		
Adequate randomization	Yes	49	0.14 (-0.25,0.53)	0.506	31	0.36 (-2.14, 3.03)	0.95	11	2.92 (-9.96,15.78)	0.55	15	0.07 (-4.45,4.34)	0.35	36	*0.48* (0.27, 0.79)	0.375	
	No	33	0.37 (-0.19,0.92)		13	0.01 (-10.42, 9.03)		7	-4.55 (-26.29,14.71)		5	-6.93 (-21.75,6.27)		15	0.77 (0.31, 1.86)		
Adequate concealment	Yes	59	0.25 (-0.08,0.58)	NA	34	0.87 (-1.43, 3.37)	NA	13	-0.81 (-6.88,5.75)	NA	16	-2.02 (-6.75,1.60)	NA	39	*0.51* (0.31, 0.79)	NA	
	No	NA	NA		NA	NA		NA	NA		NA	NA		NA	NA		
Industry funded trials	Yes	65	0.23 (-0.13,0.58)	0.877	35	0.72 (-2.02, 3.52)	0.36	13	-0.71 (-6.86,5.72)	0.66	16	-0.62 (-4.94,2.69)	1.00	39	*0.55* (0.33, 0.92)	0.484	
	No	10	0.32 (-0.78,1.39)		6	-4.57 (-15.20, 6.66)		5	-4.59 (-18.01,14.04)		4	-0.62 (-10.78,10.11)		6	0.77 (0.09, 3.75)		
Loss to follow-up	High ($\geq 20\%$)	60	*0.53* (0.08,0.98)	0.074	34	-0.39 (-5.45, 4.52)	0.51	14	1.40 (-3.77, 8.21)	0.21	15	-3.31 (-8.10,1.48)	0.66	37	0.63 (0.36, 1.11)	0.790	
	Low (<20%)	22	-0.09 (-0.64,0.38)		10	0.86 (-3.74, 6.97)		4	-18.49 (-51.56,8.85)		5	0.32 (-17.97,13.13)		14	0.79 (0.13, 2.97)		
Study design	Enrichment	22	-0.65 (-1.65,0.35)	0.093	NA	NA	NA	3	-22.92 (-61.99,16.11)	0.24	3	-14.19 (-40.56,12.39)	0.36	NA			
	Non-enrichment	60	0.25 (-0.07,0.57)		34	0.37 (-2.57, 3.19)		15	0.55 (-5.34, 7.41)		17	-1.54 (-6.21,2.32)		NA			

All values in bold are statistically significant at the 0.05 significance level. * = unless otherwise indicated. Results are cannabis for medical use versus opioids. p-value based on test of interaction

eTable 8. Subgroup analysis for secondary outcomes with low certainty evidence

Subgroup factors		Emotional functioning				Sleep quality				Discontinuations due to AEs (enriched studies)			
		No studies	WMD	95% CrI	p-value	No studies	WMD	95% CrI	p-value	No studies	OR	95% CrI	p-value
Clinical condition	Neuropathic	10	0.15	(−4.07, 4.56)	0.783	10	−3.44	(−12.56, 6.03)	0.323	4	NA	NA	NA
	Non-neuropathic	19	0.91	(−2.47, 4.08)		21	2.68	(−5.25, 10.38)		18	NA	NA	
Length of follow-up	≤ 2 months	13	0.80	(−4.77, 5.19)	0.965	16	−0.28	(−7.45, 7.26)	0.848	4			
	>2 months	17	0.93	(−2.11, 4.08)		16	0.75	(−6.96, 8.09)		18			
Adequate randomization	Yes	18	2.55	(−0.74, 5.64)	0.119	21	0.04	(−6.62, 6.70)	0.638	11	NA	NA	NA
	No	12	−1.14	(−4.54, 2.20)		11	3.21	(−8.92, 13.92)		11	2.05	(0.09, 93.28)	
Adequate concealment	Yes	22	1.44	(−0.91, 3.62)	NA	25	0.20	(−6.32, 6.44)	NA	15	0.91	(0.08, 10.88)	NA
	No	NA	NA	NA		NA	NA	NA		NA	NA	NA	
Industry funded trials	Yes	24	2.27	(−1.19, 5.68)	0.363	29	0.71	(−4.94, 6.20)	0.684	21	0.79	(0.07, 8.97)	NA
	No	5	−1.71	(−9.86, 5.86)		3	−3.12	(−20.25, 14.88)		NA	NA	NA	
Loss to follow-up	High (≥20%)	25	0.38	(−2.41, 3.04)	0.997	20	0.86	(−9.30, 10.66)	0.958	NA	NA	NA	NA
	Low (<20%)	5	0.36	(−8.02, 9.38)		12	1.13	(−11.54, 12.53)		5	0.65	(0.04, 10.18)	
Study design	Enrichment	7	4.05	(−10.97, 19.04)	0.695	6	7.27	(−4.35, 17.38)	0.184	−	−	−	−
	Non-enrichment	23	1.02	(−1.32, 3.12)		26	−1.21	(−7.49, 4.96)		−	−	−	

Results are cannabis for medical use versus opioids. Inadequate concealment not applicable because all cannabis for medical use trials had adequate concealment.

p-value based on test of interaction

eTable 9. Network meta-regression for pain outcome, length of follow-up and sample size

Pain relief, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Cannabis for medical use
Unadjusted model			
Placebo	Adjusted model		-0.60 (-0.87, -0.33)
		-1.39 ¹ (-2.04, -0.76)	
		-1.21 ² (-1.53, -0.91)	0.18 ³ (-0.55, 0.89)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		-0.60 (-0.87, -0.33)
		-0.91 ¹ (-1.37, -0.46)	
		-0.97 ² (-1.15, -0.78)	-0.06 ³ (-0.54, 0.44)

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

eTable 10. Network meta-regression for secondary outcomes, length of follow-up and sample size

Physical functioning, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Cannabis for medical use
Unadjusted model			
Placebo	Adjusted model		2.52 (0.37, 4.91)
		7.23 ¹ (2.10, 12.77)	
		3.00 ² (0.43, 5.84)	-4.20 ³ (-10.32, 1.54)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		2.52 (0.37, 4.91)
		4.19 ¹ (0.94, 7.57)	
		2.75 ² (1.16, 4.65)	-1.44 (-5.08, 2.33)

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

Emotional functioning, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Cannabis for medical use
		Unadjusted model	
Placebo	Adjusted model		0.70 (-1.42, 2.84)
Cannabis for medical use		0.96 ¹ (-4.81, 6.57)	
Opioids		0.32 ² (-2.68, 3.59)	-0.67 ³ (-6.78, 5.92)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		0.70 (-1.42, 2.84)
Cannabis for medical use		1.11 ¹ (-2.04, 4.24)	
Opioids		0.59 ² (-0.99, 2.31)	-0.50 ³ (-3.98, 3.06)

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

Role functioning, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Cannabis for medical use
		Unadjusted model	
Placebo	Adjusted model		0.88 (-3.78, 6.05)
Cannabis for medical use		14.41 ¹ (-0.89, 31.01)	
Opioids		2.22 ² (-2.95, 8.49)	-12.11 ³ (-29.35, 4.07)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		0.88 (-3.78, 6.05)
Cannabis for medical use		5.40 ¹ (-5.80, 16.94)	
Opioids		2.25 ² (-0.87, 5.72)	-3.13 ³ (-14.98, 8.65)

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

Social functioning, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Cannabis for medical use
		Unadjusted model	
Placebo	Adjusted model		1.70 (-3.28, 8.13)
Cannabis for medical use		2.43 ¹ (-7.21, 12.74)	
Opioids		1.98 ² (-3.14, 6.89)	-0.37 ³ (-11.76, 10.10)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		1.70 (-3.28, 8.13)
Cannabis for medical use		0.16 ¹ (-7.66, 8.04)	
Opioids		1.61 ² (-1.10, 4.27)	1.45 ³ (-6.89, 9.64)

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

Sleep quality, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Cannabis for medical use
Adjusted model		Unadjusted model	
		Placebo	5.95 (1.82, 10.24)
		Cannabis for medical use	-0.49 (-5.59, 4.72)
Covariate, sample size		Opioids	5.46 (2.62, 8.59)
		Placebo	8.74¹ (-1.97, 19.32)
		Cannabis for medical use	0.28 ³ (-12.32, 13.04)
Adjusted model		Opioids	9.10² (1.91, 16.26)
		Placebo	5.95 (1.82, 10.24)
		Cannabis for medical use	-0.49 (-5.59, 4.72)
Opioids		Opioids	1.16³ (-6.58, 9.00)

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

Discontinuations due to adverse events (enriched trials)			
Results are not reliable due to small number of studies. Number of studies for cannabis for medical use versus placebo = 2.			

Discontinuations due to adverse events (non-enriched trials), network estimate OR (95% CrI)			
Covariate, length of follow-up		Placebo	Cannabis for medical use
Adjusted model		Unadjusted model	
		Placebo	1.80 (1.19, 2.63)
		Cannabis for medical use	3.27 (2.71, 3.90)
Covariate, sample size		Opioids	0.75¹ (0.27, 1.84)
		Placebo	1.81 (1.21, 2.81)
		Cannabis for medical use	2.05² (1.40, 2.95)
Adjusted model		Opioids	2.70³ (1.08, 8.13)
		Placebo	1.80 (1.19, 2.63)
		Cannabis for medical use	3.27 (2.71, 3.90)
Opioids		Opioids	0.79¹ (0.32, 1.83)
		Placebo	1.81 (1.21, 2.81)
		Cannabis for medical use	2.87² (2.15, 3.79)
Opioids		Opioids	3.65³ (1.54, 9.22)

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use.

eTable 11. Network meta-analysis results for pain outcome by MME thresholds

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
-0.61 (-0.90, -0.32)	-0.31 (-0.73, 0.11)			
-0.92 (-1.23, -0.62)	-0.20 (-0.56, 0.17)	0.11 (-0.27, 0.49)		
-0.81 (-1.04, -0.58)	-0.20 (-0.58, 0.19)	0.11 (-0.28, 0.51)	0.00 (-0.34, 0.34)	
-0.81 (-1.06, -0.55)				Opioid MME 50 - 99mg

All values in bold are statistically significant at the 0.05 significance level

eTable 12. Network meta-analysis results for secondary outcomes by MME thresholds

Physical functioning				
Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
2.30 (0.35, 4.66)	-1.14 (-4.61, 1.88)			
1.14 (-1.28, 3.63)	-0.04 (-2.65, 2.59)	1.10 (-1.66, 4.36)		
2.25 (0.75, 4.26)	0.88 (-1.96, 3.56)	2.02 (-0.91, 5.28)	0.93 (-1.64, 3.29)	
3.17 (1.47, 5.23)				Opioid MME 50 - 99mg

All values in bold are statistically significant at the 0.05 significance level

Emotional functioning

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
0.66 (-1.01, 2.36)	-1.76 (-3.89, 0.44)			
-1.11 (-2.40, 0.34)	-0.59 (-2.75, 1.52)	1.17 (-0.83, 3.03)		
0.07 (-1.28, 1.42)	-1.93 (-3.87, 0.40)	-0.19 (-1.83, 1.96)	-1.36 (-2.96, 0.87)	
-1.29 (-2.35, 0.37)				Opioid MME 50 - 99mg

Role functioning

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
1.08 (-4.16, 6.90)	-3.77 (-12.25, 3.97)			
-2.70 (-8.69, 3.17)	1.72 (-5.28, 9.30)	5.47 (-1.54, 13.89)		
2.77 (-1.51, 8.36)	-0.61 (-8.18, 6.47)	3.19 (-4.34, 10.91)	-2.28 (-9.85, 3.98)	
0.48 (-4.29, 5.37)				Opioid MME 50 - 99mg

Social functioning

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
-1.33 (-5.06, 1.68)	-0.58 (-5.42, 4.77)			
-1.91 (-5.87, 1.82)				
-0.35 (-4.96, 4.41)	1.00 (-4.44, 7.11)	1.57 (-4.33, 7.76)		
1.93 (-1.13, 5.82)	3.26 (-0.97, 8.96)	3.84 (-0.81, 9.61)	2.30 (-3.22, 8.34)	

Sleep quality

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
5.93 (1.82, 10.24)				
0.09 (-11.56, 11.64)	-5.86 (-18.31, 6.37)			
4.39 (-0.12, 9.36)	-1.54 (-7.72, 4.88)	4.29 (-7.92, 17.09)		
9.56 (4.73, 14.56)	3.62 (-2.87, 10.08)	9.47 (-3.02, 22.16)	5.17 (-1.77, 11.81)	

All values in bold are statistically significant at the 0.05 significance level

Discontinuations due to adverse events (enriched trials)

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
0.99 (0.10, 10.65)				
1.23 (0.71, 2.18)	1.25 (0.11, 13.76)			
1.07 (0.63, 1.80)	1.07 (0.10, 11.38)	0.87 (0.40, 1.84)		
1.52 (0.80, 2.72)	1.52 (0.13, 16.32)	1.23 (0.53, 2.73)	1.42 (0.63, 3.12)	

Discontinuations due to adverse events (non-enriched trials)

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
1.83 (1.19, 2.67)				
3.45 (2.12, 5.28)	1.88 (1.06, 3.44)			
2.92 (2.28, 3.88)	1.60 (1.01, 2.74)	0.85 (0.52, 1.51)		
4.02 (2.86, 5.31)	2.19 (1.36, 3.57)	1.17 (0.68, 1.98)	1.38 (0.86, 1.99)	

All values in bold are statistically significant at the 0.05 significance level

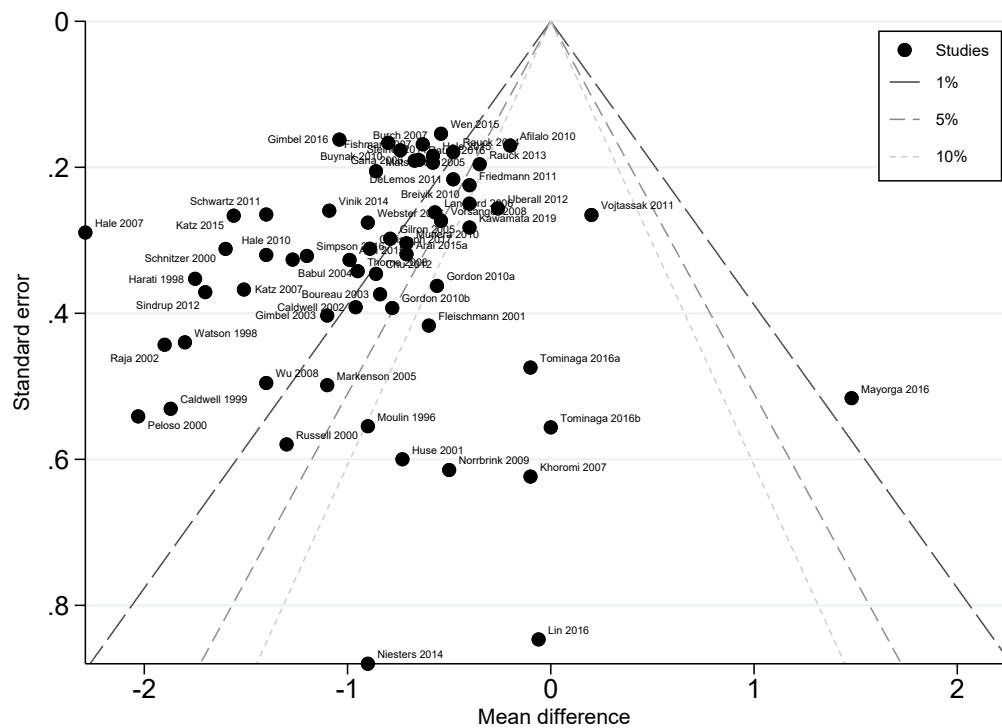
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5 **eTable 13. Pain studies from JAMA 2018 systematic review & meta-analysis included & excluded in network
6 meta-analysis**

Author	Year	Inclusion or Exclusion reason	Author	Year	Inclusion or Exclusion reason
Fleischmann	2001	Included	Schwartz	2011	Included
Bennett	2003	Combination products	Steiner	2011	Included
Ruoff	2003	Combination products	Vojtassak	2011	Included
Babul	2004	Included	Rauck	2013	Included
Emkey	2004	Combination products	Rauck	2014	Included
Peloso	2004	Combination products	Vinik	2014	Included
Gana	2006	Included	Arai	2015	Included
Webster	2006	Included	Arai	2015	Included
Burch	2007	Included	Hale	2015	Included
Fishman	2007	Included	Katz	2015	Included
Hale	2007	Included	Rauck	2015	Combination products
Katz	2007	Included	Trenkwalder	2015	Combination products
Hanna	2008	Combination products	Wen	2015	Included
Vorsanger	2008	Included	Gimbel	2016	Included
Afilalo	2010	Included	Mayorga	2016	Included
Breivik	2010	Included	Rauck	2016	Included
Buynak	2010	Included	Simpson	2016	Included
Hale	2010	Included	Tominaga	2016	Included
Katz	2010	Combination products	Tominaga	2016	Included
DeLemos	2011	Included	Christoph	2017	Included
Friedmann	2011	Included	Serrie	2017	Incomplete reporting
Total number of studies 42; 9 exclusions; 33 inclusions					

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34 **eTable 14. Pain studies included in network meta-analysis excluded from pain JAMA 2018 systematic review
35 & meta-analysis**

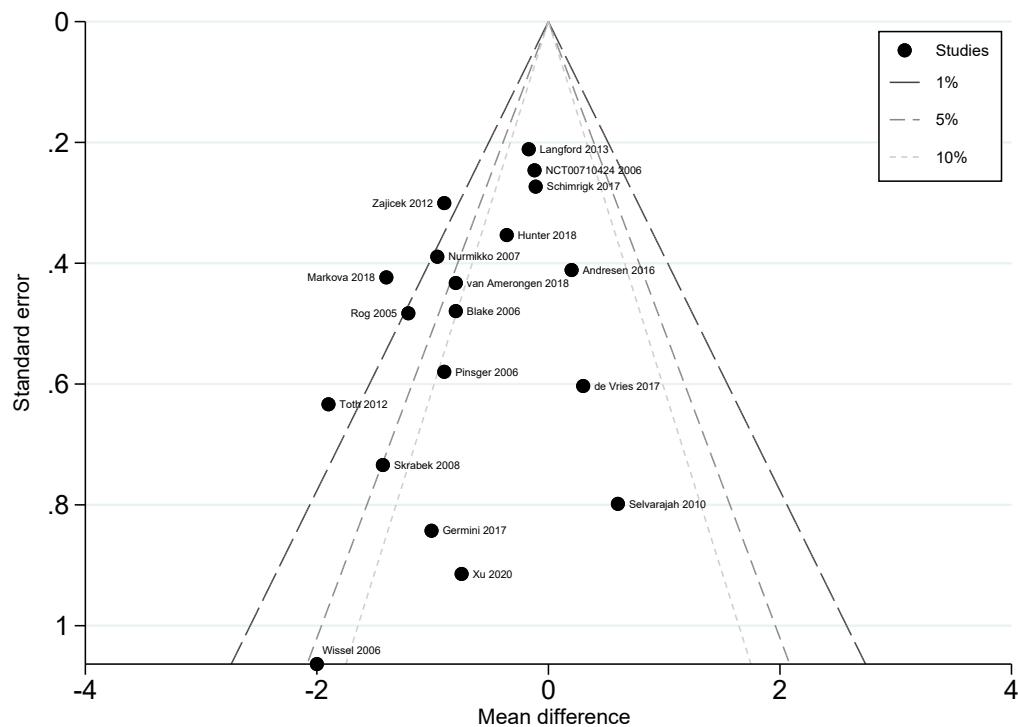
Author	Year	Exclusion reason from JAMA review	Author	Year	Exclusion reason from JAMA review
Moulin	1996	< 3months follow-up	Langford	2006	< 3months follow-up
Harati	1998	< 3months follow-up	Khoromi	2007	< 3months follow-up
Watson	1998	< 3months follow-up	Thorne	2008	< 3months follow-up
Caldwell	1999	< 3months follow-up	Wu	2008	Did not pass screening
Peloso	2000	< 3months follow-up	Norrbrink	2009	< 3months follow-up
Russell	2000	< 3months follow-up	Gordon	2010	< 3months follow-up
Schnitzer	2000	< 3months follow-up	Gordon	2010	< 3months follow-up
Huse	2001	< 3months follow-up	Munera	2010	< 3months follow-up
Caldwell	2002	< 3months follow-up	Chu	2012	< 3months follow-up
Raja	2002	< 3months follow-up	Sindrup	2012	< 3months follow-up
Boureau	2003	< 3months follow-up	Uberall	2012	< 3months follow-up
Gimbel	2003	< 3months follow-up	Niesters	2014	< 3months follow-up
Gilron	2005	< 3months follow-up	Lin	2016	< 3months follow-up
Markenson	2005	Did not pass screening	Kawamata	2019	Published after search execution end date
Matsumoto	2005	< 3months follow-up			
Total number of studies 29.					

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3 **eFigure 18. Funnel plot for pain for randomized trials of opioids versus placebo**

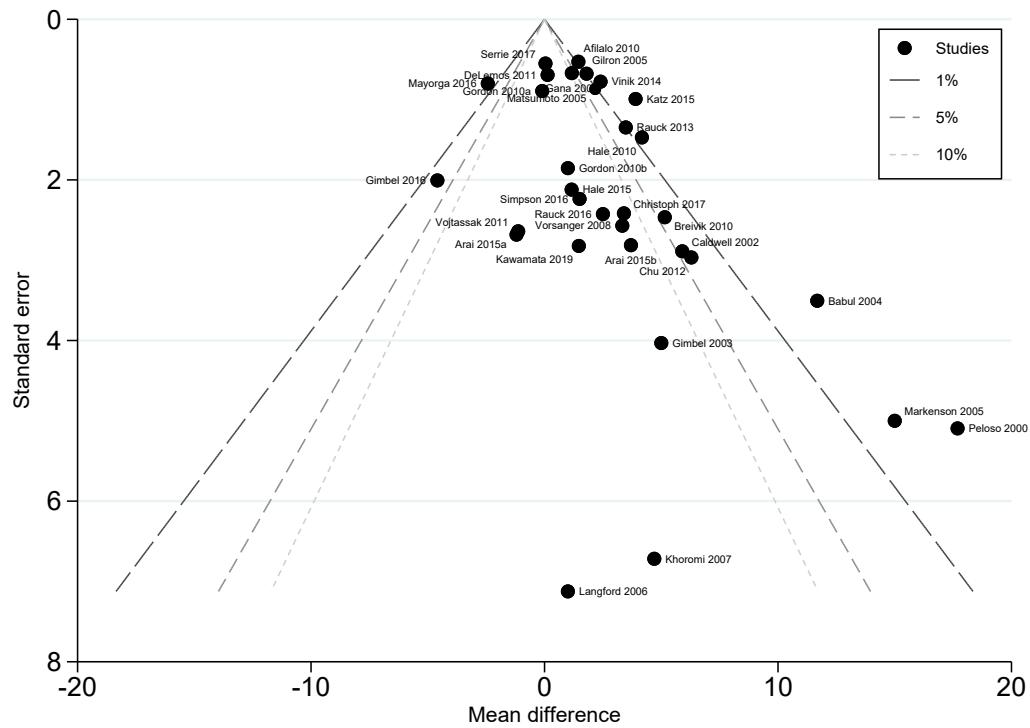


Egger's test p-value = 0.039

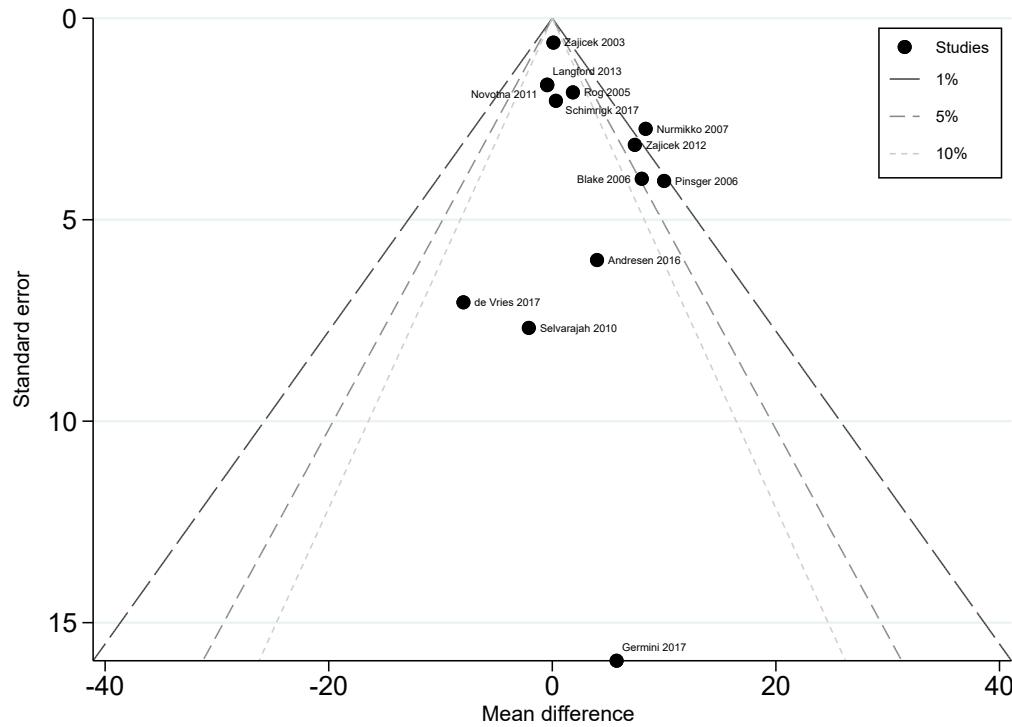
eFigure 19. Funnel plot for pain for randomized trials of cannabis for medical use versus placebo



Egger's test p-value = 0.044

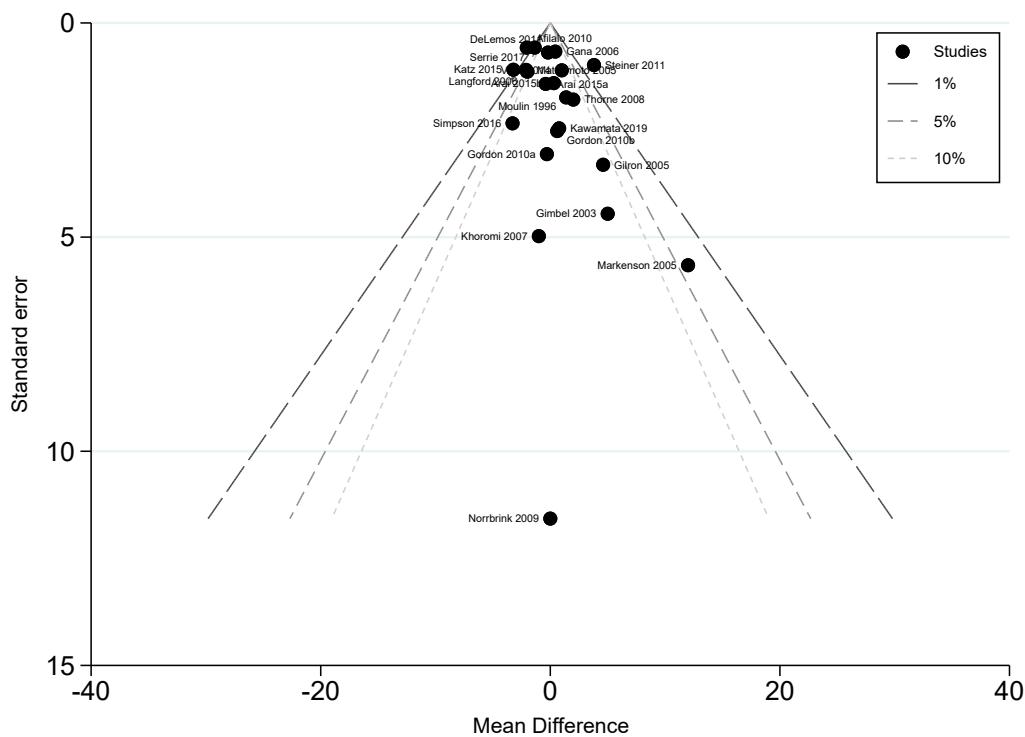
eFigure 20. Funnel plot for physical functioning for randomized trials of opioids versus placebo

Egger's test p-value = 0.015

eFigure 21. Funnel plot for physical functioning for randomized trials of cannabis for medical use versus placebo

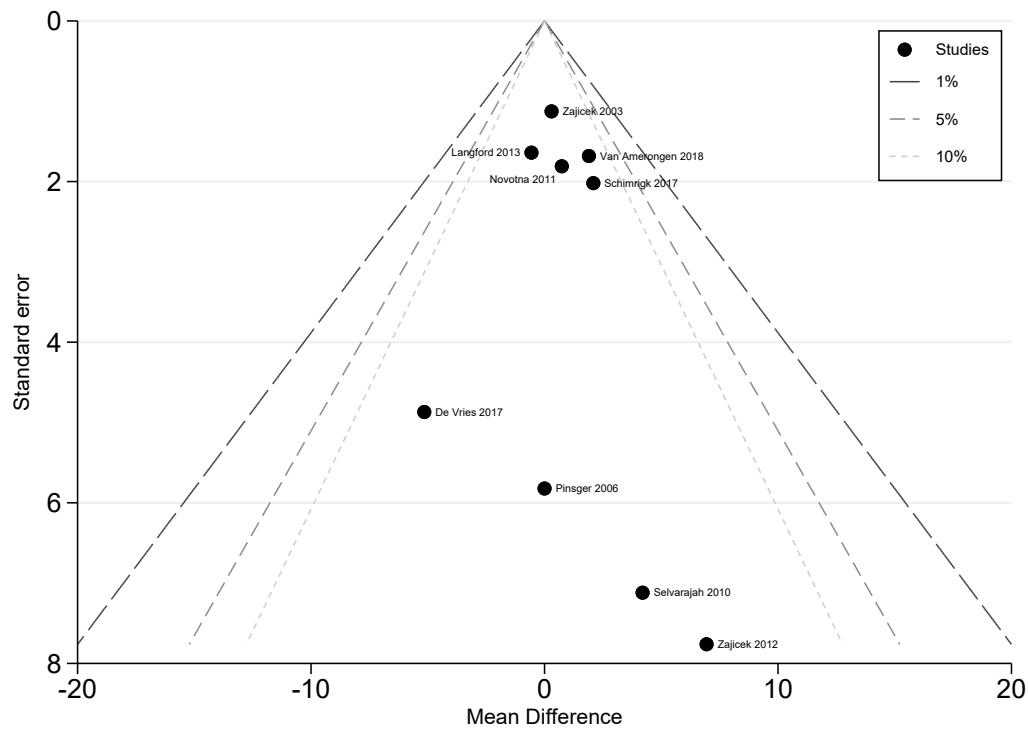
Egger's test p-value = 0.098

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5 **eFigure 22. Funnel plot for emotional functioning for randomized trials of opioids versus placebo**



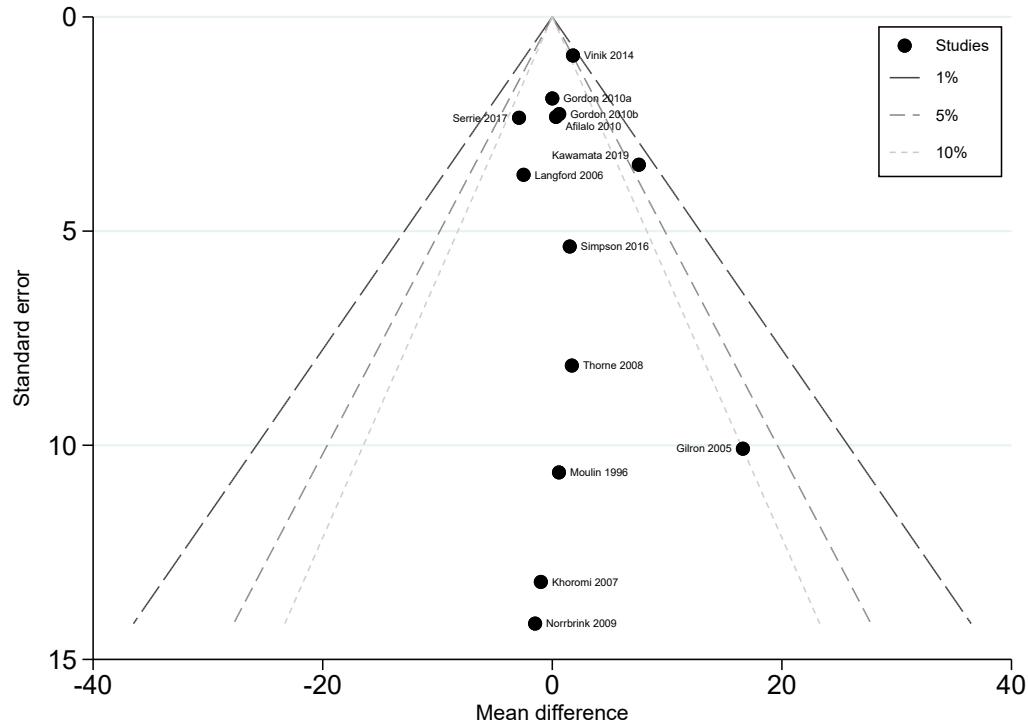
Egger's test p-value = 0.121

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3 **eFigure 23. Funnel plot for emotional functioning for randomized trials of cannabis for medical use versus**
4 **placebo**



Egger's test p-value = 0.71

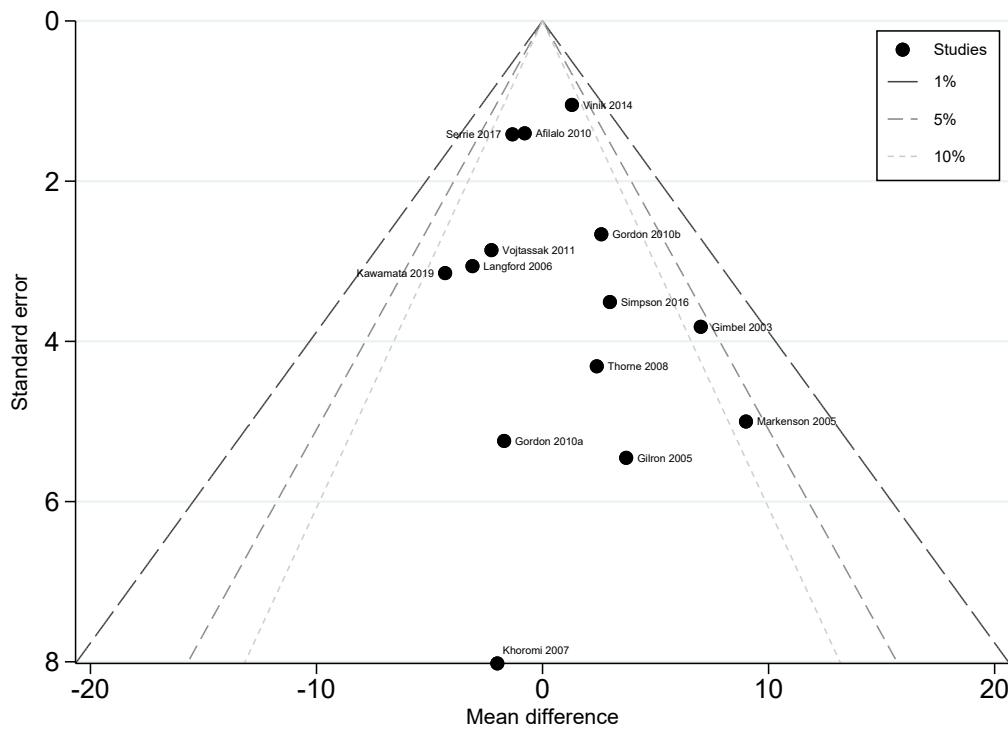
32 **eFigure 24. Funnel plot for role functioning for randomized trials of opioids versus placebo**



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3 Egger's test p-value = 0.967
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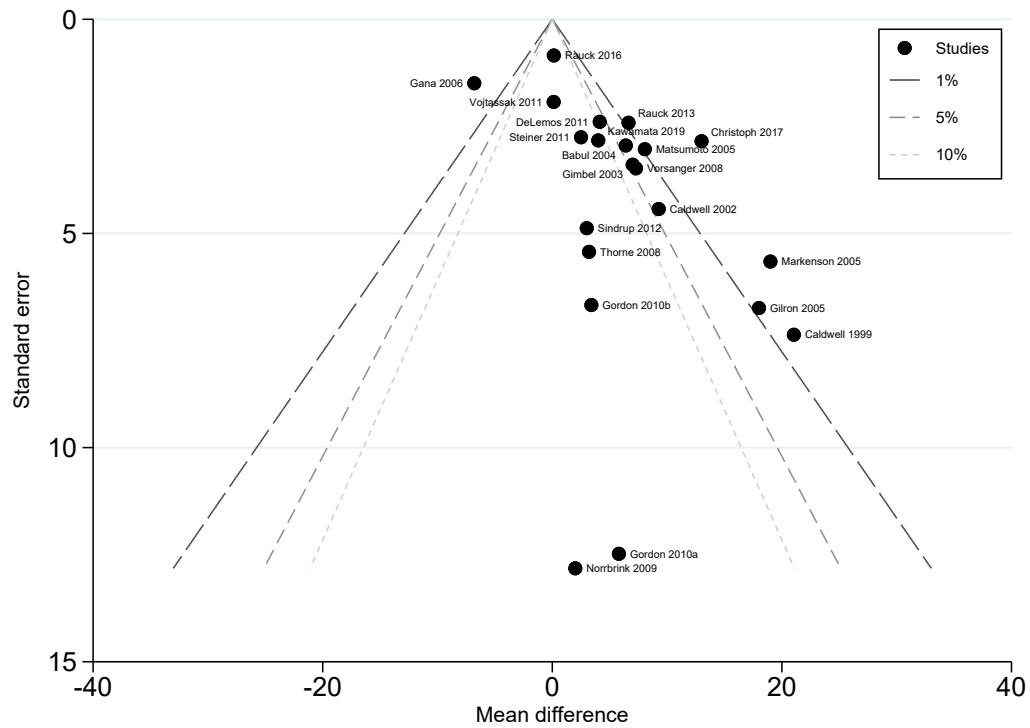
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eFigure 25. Funnel plot for social functioning for randomized trials of opioids versus placebo



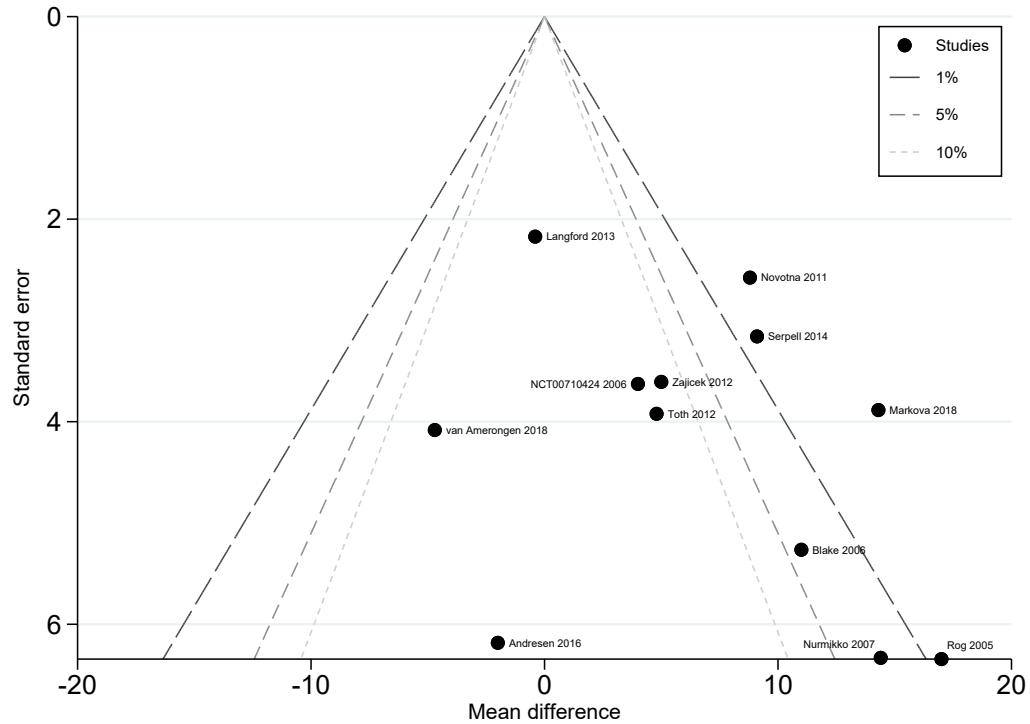
Egger's test p-value = 0.548

eFigure 26. Funnel plot for sleep quality for randomized trials of opioids versus placebo



Egger's test p-value = 0.003

eFigure 27. Funnel plot for sleep quality for randomized trials of cannabis for medical use versus placebo



Egger's test p-value = 0.258



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplement eAppendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7-8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 7-8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 7-8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 7-8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 7-8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7-9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8-9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). For peer review only - http://bmjopen.bmjjournals.org/site/about/guidelines.xhtml	Page 9



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 10
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 11 & Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1 & Supplement eAppendix 3
Study characteristics	17	Cite each included study and present its characteristics.	Supplement eTable 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplement eTable 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 10-13
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Table 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Table 3 & Supplement eTable 6-10; eFigure 19-27
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Table 3 & Supplement eTable 6-10; eFigure 19-27
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Table 3 & Supplement eTable 6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Table 2 & Supplement eTable 4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 18-19
	23b	Discuss any limitations of the evidence included in the review.	Page 20
	23c	Discuss any limitations of the review processes used.	Page 20



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	Page 20
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 10 & 23
Competing interests	26	Declare any competing interests of review authors.	Page 23
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 23

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
 For more information, visit: <http://www.prisma-statement.org/>

BMJ Open

Cannabis for medical use versus opioids for chronic noncancer pain: A systematic review and network meta-analysis of randomized clinical trials

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Keywords:	Pain management < ANAESTHETICS, Neurological pain < NEUROLOGY, Back pain < ORTHOPAEDIC & TRAUMA SURGERY, PAIN MANAGEMENT

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Cannabis for medical use versus opioids for chronic noncancer pain: A systematic review and network meta-analysis of randomized clinical trials

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ABSTRACT**OBJECTIVE**

To evaluate the comparative benefits and harms of opioids and cannabis for medical use for chronic noncancer pain.

DESIGN

Systematic review and network meta-analysis.

DATA SOURCES

EMBASE, MEDLINE, CINAHL, AMED, PsycINFO, PubMed, Web of Science, Cannabis-Med, Epistemonikos and the Cochrane Library (CENTRAL) from inception to March 2021.

STUDY SELECTION

Randomized trials comparing any type of cannabis for medical use or opioids, against each other or placebo, with patient follow-up ≥ 4 weeks.

DATA EXTRACTION AND SYNTHESIS

Paired reviewers independently extracted data. We used Bayesian random-effects network meta-analyses to summarize the evidence and the GRADE approach to evaluate the certainty of evidence and communicate our findings.

RESULTS

Ninety trials involving 22 028 patients were eligible for review, among which the length of follow-up ranged from 28 to 180 days. Moderate certainty evidence showed that opioids provide small improvements in pain, physical functioning, and sleep quality vs. placebo; low to moderate certainty evidence supported similar effects for cannabis vs. placebo. Neither were more effective than placebo for role, social or emotional functioning (all high to moderate certainty evidence). Moderate certainty evidence showed there is probably little to no difference between

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3 cannabis for medical use and opioids for physical functioning (weighted mean difference
4 [WMD] 0.47 on the 100-point SF-36 physical component summary score, 95% CrI -1.97 to
5 2.99), and cannabis resulted in fewer discontinuations due to adverse events vs. opioids (odds
6 ratio 0.55, 95% CrI 0.36 to 0.83). Low certainty evidence suggested little to no difference
7 between cannabis and opioids for pain relief (WMD 0.23cm on a 10cm visual analogue scale
8 [VAS], 95% CrI -0.06 to 0.53) or sleep quality (WMD 0.49mm on a 100mm VAS, 95% CrI -
9 4.72 to 5.59).

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19 **CONCLUSIONS**
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22 Cannabis for medical use may be similarly effective and result in fewer discontinuations than
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24 opioids for chronic noncancer pain.
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6 Strengths and limitations of this study
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- 10 • A Bayesian random-effects network meta-analyses was used to evaluate the comparative
11 effectiveness of cannabis for medical use and opioids for management of chronic
12 noncancer pain.
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 - 14 • We conducted a comprehensive search for eligible trials and used the GRADE approach
15 to appraise the certainty of evidence for treatment effects and focused our analysis on
16 patient-important outcomes.
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 - 18 • Twenty-four RCTs evaluating cannabis for medical use were included in our review;
19 however, none of these trials administered inhaled forms of cannabis and the
20 generalizability of our findings to smoked or vaporized cannabis is uncertain.
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 - 22 • For the comparison of cannabis for medical use and opioids, the majority of our
23 outcomes were informed by indirect evidence since we found only one trial directly
24 comparing both interventions for chronic pain.
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Introduction

Chronic noncancer pain impacts 20% of the global population and is associated with reduced quality of life, disability, and considerable socioeconomic burden [1-4]. Opioids are commonly prescribed for chronic noncancer pain and may provide improvement in pain relief, physical functioning and quality of sleep compared to placebo [5]; however, they are also associated with harms including addiction, overdose and death [6,7]. There is growing interest in cannabis as an alternative to long-term opioid use [8], and countries increasingly permit therapeutic use of cannabis [9]. Two-thirds of cannabis for medical use users endorse management of chronic pain as their indication for use [10]. Despite increasing availability of cannabis for medical use its' use for chronic pain remains controversial due, in part, to conflicting recommendations. A 2019 guideline from the National Institute for Health and Care Excellence (NICE) made strong recommendations against use of cannabis for chronic pain, and in 2021 the International Association for the Study of Pain (IASP) released a position statement against the use of cannabinoids for pain [11,12]. Alternately, a 2021 BMJ Rapid Recommendation made a conditional recommendation to offer a trial of non-inhaled cannabis for medical use for people living with chronic pain if standard care was insufficient [13]. The European Pain Federation (EFIC) also issued a position paper stating that cannabis based medicines can be used by experienced physicians when guideline recommended 1st and 2nd line therapies for chronic pain do not provide sufficient benefit [14]. We undertook a systematic review and network meta-analysis of randomized controlled trials (RCTs) to explore the comparative benefits and harms of cannabis for medical use and opioids for chronic noncancer pain.

Methods

We adhered to the Preferred Reporting items for Systematic reviews and Meta-Analyses extension statement for network meta-analysis (PRISMA-NMA) [15], registered our review on PROSPERO (CRD42020185184) [16], and followed GRADE guidance for communicating our findings [17].

Data Sources and Searches

We searched EMBASE, MEDLINE, CINAHL, AMED, PsycINFO, PubMed, Web of Science, Cannabis-Med, Epistemonikos and the Cochrane Library (CENTRAL) from inception to March 2021, without language restrictions, including grey literature from clinicaltrials.gov. An experienced medical librarian developed database-specific search strategies (eAppendix 1 in Supplement). We reviewed reference lists of eligible studies, and relevant reviews and guidelines, to identify additional studies. We included RCTs that enrolled ≥ 20 patients with chronic noncancer pain (pain lasting ≥ 3 months), randomized them to any type of cannabis for therapeutic use, an opioid, or placebo and followed them for ≥ 4 weeks to allow for sufficient time for functional outcomes to manifest among treatment responders [13]. Trials including patients with chronic cancer and noncancer pain were included if outcome data were reported separately. We excluded conference abstracts and trials of combination products (e.g., opioids with nonsteroidal anti-inflammatory drugs or anti-depressants).

Pairs of reviewers independently screened titles and abstracts, and full text reports, and extracted data using standardized, pilot-tested forms using online systematic review software (DistillerSR, Evidence Partners, Ottawa, Canada; <http://systematic-review.net/>). For all eligible trials, we (W.L., N.A. C.R, J.H.M) collected information regarding study characteristics, intervention

details, patient characteristics, and all patient-important outcomes as guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials [18,19]. Discrepancies were resolved by discussion or, when necessary, by an adjudicator.

Risk of Bias Assessment

Risk of bias was assessed for eligible studies, independently and in duplicate, by pairs of reviewers using a modified Cochrane risk of bias instrument (RoB 1.0) according to the following domains: random sequence generation, allocation concealment, blinding of participants, caregivers, outcome assessors, and data analysts, and loss to follow-up ($\geq 20\%$ missing data was considered high risk of bias) [20,21].

Data Analysis

Instruments used in the RCTs mostly consisted of the visual analogue scale (VAS) and the numerical rating scale (NRS) for measuring pain intensity and sleep quality, and the Short Form-36 for other important patient outcomes (e.g. physical functioning, emotional functioning, role functioning, social functioning). These instruments have been shown to be reliable and valid in chronic pain populations [22-24]. eTable 1 lists additional instruments that were used to capture patient-important outcomes, and references supporting their psychometric properties. We converted continuous measures to common scales on a domain-by-domain basis when different instruments were used to measure the same construct by re-scaling the mean and SD of the other instruments: (1) pain relief to a 10cm visual analogue scale (VAS); (2) physical functioning to the 100-point 36-item Short Form Survey (SF-36) physical component summary (PCS) score; (3) emotional functioning to the 100-point SF-36 mental component summary (MCS) score; (4) role

functioning to the 100-point SF-36 subscale for role limitations due to physical problems; (5) social functioning to the 100-point SF-36 subscale for social functioning; and (6) sleep quality to a 100-mm VAS [25].

We calculated direct estimates for any comparison reported by two or more studies as the weighted mean difference (WMD) and associated 95% credible interval (95% CrI) using change score from baseline to the end of follow-up to address interpatient variability. When standard deviations (SDs) for continuous outcomes were not reported by study authors, they were estimated using confidence intervals or exact p-values [26]. To optimize interpretability of our findings for statistically significant continuous outcomes, we used the network estimate of treatment effects to model the risk difference (RD) for achieving the minimally important difference (MID) or higher. We used an MID of 1cm for the 10-cm VAS for pain [27], 10mm for sleep quality, 10-points for SF-36 subscales (role and social functioning), and 5-points for SF-36 PCS and MCS scores [28,29].

For discontinuations due to adverse events, we used a binomial likelihood distribution and logit link to generate the pooled odds ratio (OR) with corresponding 95% CrI. We constructed separate models for enriched and non-enriched trials, as enriched trials typically exclude patients who report problematic adverse events during an open-label run-in period prior to randomization [30]. For estimating the number of patients expected to discontinue due to adverse events, we calculated the absolute effects for network estimates by multiplying the OR and its 95% CrI with the estimated baseline risk for discontinuations due to adverse events. We used median risk in the placebo group of included randomized trials as the baseline risk.

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5 For studies that reported outcomes at several timepoints, we used data from the longest follow-
6 up. We performed all conventional pairwise meta-analyses using DerSimonian and Laird
7 random-effects models. Heterogeneity between RCTs for each direct comparison was assessed
8 with visual inspection of forest plots and the I^2 statistic [31]. For all direct comparisons, we
9 assessed small study effects using funnel plots and Egger's test when 10 or more trials were
10 available [32].
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22 The feasibility of conducting a random effects Bayesian NMA was assessed for all outcomes –
23 this included assessing homogeneity of included studies, patients, and intervention
24 characteristics, and network connectivity. We used edge-splitting (side-splitting) to evaluate the
25 consistency of relative treatment effects between direct (e.g. pairwise meta-analysis) and indirect
26 evidence, and leverage plots to visually inspect model fit [33]. Models were programmed with
27 three chains, and the convergence assessed using the Gelman-Rubin statistic [34]. All analyses
28 began with a burn-in phase (1000 iterations) followed by 100 000 iterations with 1000
29 adaptations. We used non-informative priors with mean 0 and standard deviation $15u$, where u is
30 the largest maximum likelihood estimator of treatment differences on the linear scale in single
31 trials [35]. Statistical superiority was asserted when the 95% CrI excluded the null effect (i.e., 0.0
32 for WMDs and 1.0 for ORs). All analyses were programmed in R v3.5.3 ([https://www.R-](https://www.R-project.org)
33 project.org) using BUGSnet [35].
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We tested the following a priori subgroup hypotheses that treatment effects were associated with:
(1) neuropathic vs. non-neuropathic pain; (2) shorter vs. longer (≤ 2 months vs > 2 months)

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3 follow-up; (3) trials at risk of bias (on a criterion-by-criterion basis); (4) enriched enrollment
4 trials vs not enriched; and (5) higher opioid doses versus lower opioid doses by evaluating the
5 following morphine milligram equivalent (MME) per day thresholds: (i) high = MME > 100 mg;
6 (ii) intermediate = MME 50 – 99 mg; and (iii) low = MME < 50 mg. We assessed the credibility
7 of significant subgroup effects (i.e., test of interaction $p \leq 0.05$) with the ICEMAN tool [36]. We
8 used network meta-regression to explore the association between treatment effects and length of
9 follow-up and sample size. The deviance information criterion (DIC) was used to assess model
10 fit.
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24 **Quality of Evidence**

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26 We used the Grading of Recommendations, Assessment, Development and Evaluations
27 (GRADE) approach to assess certainty of the evidence for all outcomes and effect estimates from
28 network meta-analysis [37]. Ratings of the certainty of evidence for direct and indirect estimates
29 included assessment of risk of bias, inconsistency, indirectness, publication bias, and
30 intransitivity (only for indirect estimates). We judged network estimates as imprecise if the 95%
31 CrI included half the MID for continuous outcomes (e.g., 0.5 cm for pain) or the null effect (OR
32 of 1) for discontinuation due to adverse events.

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43 **Role of the funding source**

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45 The funders had no role in study design, data collection, analysis, interpretation or writing of the
46 manuscript, or the decision to submit.

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53 **Patient and Public Involvement**

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55 Patients and public were not involved in this research.

Results

Of 20 012 citations identified, 90 studies from 89 publications proved eligible for review (Figure 1, eAppendix 2-3 in Supplement). No trials of inhaled cannabis were eligible for our review due to inadequate duration of follow-up (<4 weeks). Sixty-six trials compared opioids to placebo [38-102], 23 trials compared cannabis for medical use to placebo [103-125], and 1 trial [126] randomized patients to nabilone or dihydrocodeine. The evidence network for all our outcomes are presented in Figure 2. Among the included studies, the median of the mean age of participants was 56 years (interquartile range [IQR] 50 to 62), 58% were female, the median of the mean duration of pain was 8.1 years (IQR 5.0 to 12.7), and the median of the mean pain score at enrollment was 6.05 (IQR 4.65 to 6.90). Twenty-nine trials enrolled patients with neuropathic pain, 60 with non-neuropathic pain, and 1 trial enrolled patients with mixed pain. (Table 1, & eTable 2 in Supplement for details on the pain conditions and other baseline characteristics).

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Table 1: Summary of study participant characteristics included in eligible randomized
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control trials

No of trials	No of patients	Age, median of mean (IQR)	% female, median of mean (IQR)	Baseline pain score, median of mean (min – max)	No of studies by pain type*	No of studies by Intervention dose/format*	Follow-up, median days (min – max)	Trial type*
Opioids versus placebo								
66	18,401	58 (50 to 62)	56 (44.5 to 62)	6.01 (1.87-7.83)	Neuropathic pain, n = 18 (27%) Non-neuropathic, n = 47 (71%) Mixed, n = 1 (2%)	MME > 90mg, n = 14 (21%) MME 50 – 90mg, n = 19 (29%) MME < 50 mg, n = 21 (32%) Dose details Not reported n = 12 (18%)	84 (28–180)	Enriched n = 20 (30%) Non-enriched n = 46 (70%)
Cannabis for medical use versus placebo								
23	3,435	53 (50 to 58)	62 (40 to 70)	6.28 (2.15–7.80)	Neuropathic pain, n = 10 (43%) Non-neuropathic, n = 13 (57%)	PEA, n = 2 (9%) THC/CBD, n = 11 (48%) THC, n = 7 (30%) CBD n = 2 (9%) CBDV n = 1 (4%)	51 (28–112)	Enriched n = 3 (13%) Non-enriched n = 20 (87%)
Cannabis for medical use versus opioids								
1	192	50	26	6.72	Neuropathic pain, n = 1 (100%)	THC, n = 1 (100%)	42	Non-enriched n = (100%)

31 * Values in parenthesis are percentage of trials

32 **IQR, interquartile range.

33 CBDV, Cannabidiolvarin

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5 Most trials (75 of 90; 83%) were judged to be at high risk of bias for at least one domain.
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7 Adequate generation of a randomization sequence was reported by 53 (59%) trials, 64 (71%)
8 reported concealment of allocation, and almost all trials reported blinding of patients (99%) and
9 healthcare providers and data collectors (98%). (eTable 3 in Supplement). Sixty-five (72%) trials
10 reported $\geq 20\%$ missing outcome data. (eTable 3 in Supplement). We did not find evidence of
11 incoherence. For closed loop networks, consistency was met based on DIC values. For open loop
12 networks, direct and indirect estimates are reported separately. (eTable 4,5 & eFigure 1 in
13 Supplement).
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26 Moderate certainty evidence showed that, compared to placebo, opioids provide small
27 improvements in pain (modelled RD for achieving the MID 15%, 95% CrI 13 to 17), physical
28 functioning (modelled RD for achieving the MID 5%, 95% CrI 3 to 8), and sleep quality
29 (modelled RD for achieving the MID 8%, 95% CrI 4 to 13). Low to moderate certainty evidence
30 supported similar effects for cannabis for medical use vs. placebo. Neither were more effective
31 than placebo for role, social, or emotional functioning (all high to moderate certainty evidence).
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33 (Table 2, eTable 4 &, eFigure 2-13 in Supplement).
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45 Low certainty evidence from 82 RCTs involving 19 693 patients suggested that there may be
46 little to no difference in pain relief between cannabis for medical use and opioids (WMD 0.23cm
47 on a 10cm VAS, 95% CrI -0.06 to 0.53). (Table 2, eFigure 1 & eTable 4 in Supplement).
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49 Moderate certainty evidence from 44 RCTs involving 12 727 patients shows there is probably
50 little to no difference in physical functioning with cannabis for medical use compared to opioids
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(WMD 0.47 points on the 100-point SF-36 PSC score, 95% CrI -1.97 to 2.99). (Table 2, eTable 4 in Supplement). Low certainty evidence from 32 RCTs involving 8 201 patients suggests that there may be little to no difference in sleep quality between cannabis for medical use and opioids (WMD 0.49mm on a 100mm VAS, 95% CrI -4.72 to 5.59). (Table 2, eTable 4 in Supplement). There were insufficient data to construct networks for health-related quality of life (eAppendix 4 in Supplement).

Discontinuations due to adverse events were reported in 22 enrichment trials (6 831 patients) and in 51 non-enrichment trials (13 012 patients). Among enrichment trials, low certainty evidence suggests that there may be little to no difference in discontinuations due to adverse events between cannabis for medical use and opioids (OR 0.77, 95% CrI 0.07 to 8.83). Moderate certainty evidence shows that in non-enriched studies, discontinuations due to adverse events are probably less for cannabis for medical use vs. opioids (OR 0.55, 95% CrI 0.36 to 0.83). (Table 2). Moderate and high certainty evidence showed that, compared to placebo, opioids and cannabis for medical use, respectively, probably results in higher discontinuations compared to placebo (modelled RD for achieving the MID for opioids vs. placebo, 10%, 95% CrI 8% to 12%; cannabis for medical use vs. placebo, 4%, 95% CrI 1% to 7%). (Table 2, eFigure 14-17 in Supplement).

We found no evidence of credible subgroup effects based on type of pain condition (neuropathic versus non-neuropathic), length of follow-up, sample size, or opioid dose (Table 3, eTable 6-12 in Supplement).

Table 2: Treatment effects and certainty of evidence (GRADE) for opioids and cannabis for medical use in patients with chronic noncancer pain

Comparison	Direct evidence		Indirect evidence		Network estimate WMD (95% CrI)	RD for achieving the MID (95% CI)	GRADE
	no. of trials (patients)	Treatment effect WMD* (95% CI)	no. of trials (patients)	Treatment effect WMD* (95% CI)			
Pain relief: 10cm VAS for pain; lower is better; MID = 1cm							
Opioids vs. placebo	62 (17,431)	-0.84 (-0.99 to -0.69)	62 (17,431)	-0.83 (-0.97 to -0.70)	-0.83 (-0.97 to -0.70)	15% (13% to 17%)	Moderate
Cannabis for medical use vs. placebo	19 (2,116)	-0.63 (-0.94 to -0.32)	19 (2,116)	-0.59 (-0.88 to -0.32)	-0.60 (-0.87 to -0.33)	11% (6% to 15%)	Low
Cannabis for medical use vs. opioids	1 (146)	0.13 (-0.54 to 0.80)	81 (19,547)	0.24 (-0.07 to 0.55)	0.23 (-0.06, 0.53)	-	Low
Physical functioning: 0-100 point SF-36 PCS score; higher is better; MID = 5-points							
Opioids vs. placebo	32 (10,926)	2.38 (1.05 to 3.72)	-	-	2.05 (1.01, 3.29)	5% (3% to 8%)	Moderate
Cannabis for medical use vs. placebo	12 (1,801)	3.00 (0.08 to 5.91)	-	-	2.52 (0.37, 4.91)	6% (1% to 12%)	Moderate
Cannabis for medical use vs. opioids	-	-	44 (12,727)	0.47 (-1.97 to 2.99)	0.47 (-1.97 to 2.99)	-	Moderate
Emotional functioning: 0-100 point SF-36 MCS score; higher is better; MID = 5-points							
Opioids vs. placebo	22 (7,267)	-0.00 (-1.09 to 1.09)	-	-	-0.15 (-1.10 to 0.92)	-	High
Cannabis for medical use vs. placebo	8 (1,515)	0.72 (-1.01 to 2.45)	-	-	0.70 (-1.42 to 2.84)	-	Moderate
Cannabis for medical use vs. opioids	-	-	30 (8,782)	0.85 (-1.55 to 3.18)	0.85 (-1.55 to 3.18)	-	Low
Role functioning: 0-100 point SF-36 subscale for role limitations due to physical problems; higher is better; MID = 10-points							
Opioids vs. placebo	13 (3,661)	0.91 (-1.17 to 2.98)	-	-	0.94 (-1.26 to 3.17)	-	Moderate
Cannabis for medical use vs. placebo	5 (528)	1.27 (-12.39 to 14.93)	-	-	0.88 (-3.78 to 6.05)	-	Moderate
Cannabis for medical use vs. opioids	-	-	18 (4,189)	-0.05 (-5.16 to 5.60)	-0.05 (-5.16 to 5.60)	-	Moderate
Social functioning: 0-100 point SF-36 subscale for social functioning; higher is better; MID = 10-points							
Opioids vs. placebo	14 (4,075)	0.47 (-1.47 to 2.41)	-	-	1.17 (-1.72 to 4.58)	-	Moderate
Cannabis for medical use vs. placebo	6 (795)	-1.82 (-5.79 to 2.15)	-	-	1.70 (-3.28 to 8.13)	-	Moderate
Cannabis for medical use vs. opioids	-	-	20 (4,870)	0.55 (-5.34 to 7.41)	0.55 (-5.34 to 7.41)	-	Moderate
Sleep quality: 100mm VAS for sleep quality; higher is better; MID = 100mm							
Opioids vs. placebo	21 (6,677)	5.55 (2.67 to 8.43)	-	-	5.46 (2.62 to 8.59)	8% (4% to 13%)	Moderate
Cannabis for medical use vs. placebo	11 (1,524)	6.04 (1.43 to 10.66)	-	-	5.95 (1.82 to 10.24)	9% (3% to 15%)	Low
Cannabis for medical use vs. opioids	-	-	32 (8,201)	0.49 (-4.72 to 5.59)	0.49 (-4.72 to 5.59)	-	Low
Discontinuations due to adverse events (enriched trials)							
Opioids vs. placebo	20 (6,699)	OR, 1.39 (1.04 to 1.86)	-	-	OR, 1.25 (0.91, 1.67)	-	Low

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3	Cannabis for medical use vs. placebo	2 (132)	OR, 5.00 (0.25 to 101.7)		-	OR, 0.96 (0.09 to 10.80)	
4							Low
5	Cannabis for medical use vs. opioids		-	22 (6,831)	OR, 0.77 (0.07 to 8.83)	OR, 0.77 (0.07 to 8.83)	
6							Low
7	Discontinuations due to adverse events (non-enriched trials)						
8	Opioids vs. placebo	35 (11,019)	OR, 3.58 (3.00 to 4.27)	35 (11,019)	OR, 3.27 (2.70 to 3.93)	OR, 3.27 (2.71 to 3.90)	10% (8% to 12%)
9							Moderate
10	Cannabis for medical use vs. placebo	15 (1,801)	OR, 2.47 (1.49 to 4.11)	15 (1,801)	OR, 1.78 (1.15 to 2.63)	OR, 1.80 (1.19 to 2.63)	4% (1% to 7%)
11							High
12	Cannabis for medical use vs. opioids	1 (192)	OR, 0.50 (0.16, 1.61)	50 (12,820)	OR, 0.54 (0.34 to 0.84)	OR, 0.55 (0.36 to 0.83)	
13							Moderate
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15	OR = odds ratio. RD = risk difference and represents the percentage of patients achieved at or above MID. WMD = weighted mean difference						
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Table 3: Subgroup analysis for pain and secondary outcomes with moderate to high certainty evidence

Subgroup factors		Pain relief	Physical functioning	Role functioning	Social functioning	Discontinuations due to adverse events (non-enriched)
		WMD 95% CrI	WMD 95% CrI	WMD 95% CrI	WMD 95% CrI	OR 95% CrI
Clinical condition	Neuropathic	0.74 (0.30,1.12)	-0.67 (-4.46, 3.28)	-4.66 (-21.16,5.49)	-8.09 (-16.89,-0.69)	0.91 (0.48, 1.76)
	Non-neuropathic	-0.12 (-0.55,0.30)	0.97 (-2.67, 4.72)	9.81 (-1.55,21.10)	1.01 (-3.01,4.75)	*0.34* (0.15, 0.67)
Length of follow-u	≤ 2 months	0.04 (-0.36,0.45)	2.35 (-2.72,6.56)	8.59 (-3.64,20.37)	-0.31 (-8.27,7.79)	*0.42* (0.20, 0.79)
	>2 months	0.41 (-0.04,0.85)	-0.75 (-3.83, 2.38)	-2.48 (-11.89, 5.23)	-2.26 (-9.50,2.29)	0.65 (0.37, 1.16)
Adequate randomization	Yes	0.14 (-0.25,0.53)	0.36 (-2.14, 3.03)	2.92 (-9.96,15.78)	0.07 (-4.45,4.34)	*0.48* (0.27, 0.79)
	No	0.37 (-0.19,0.92)	0.01 (-10.42, 9.03)	-4.55 (-26.29,14.71)	-6.93 (-21.75,6.27)	0.77 (0.31, 1.86)
Adequate concealment	Yes	0.25 (-0.08,0.58)	0.87 (-1.43, 3.37)	-0.81 (-6.88,5.75)	-2.02 (-6.75,1.60)	*0.51* (0.31, 0.79)
	No	NA	NA	NA	NA	NA
Industry funded trials	Yes	0.23 (-0.13,0.58)	0.72 (-2.02, 3.52)	-0.71 (-6.86,5.72)	-0.62 (-4.94,2.69)	*0.55* (0.33, 0.92)
	No	0.32 (-0.78,1.39)	-4.57 (-15.20, 6.66)	-4.59 (-18.01,14.04)	-0.62 (-10.78,10.11)	0.77 (0.09, 3.75)
Loss to follow-up	High (≥20%)	*0.53* (0.08,0.98)	-0.39 (-5.45, 4.52)	1.40 (-3.77, 8.21)	-3.31 (-8.10,1.48)	0.63 (0.36, 1.11)
	Low (<20%)	-0.09 (-0.64,0.38)	0.86 (-3.74, 6.97)	-18.49 (-51.56,8.85)	0.32 (-17.97,13.13)	0.79 (0.13, 2.97)
Study design	Enrichment	-0.65 (-1.65,0.35)	NA	-22.92 (-61.99,16.11)	-14.19 (-40.56,12.39)	NA
	Non-enrichment	0.25 (-0.07,0.57)	0.37 (-2.57, 3.19)	0.55 (-5.34, 7.41)	-1.54 (-6.21,2.32)	

All values in bold are statistically significant at the 0.05 significance level. * = unless otherwise indicated. Results are cannabis for medical use versus opioids. Pain relief for neuropathic pain vs non-neuropathic p-value = 0.004. Social functioning for neuropathic pain vs non-neuropathic p-value = 0.047. p-value based on test of interaction. Number of studies and p-values for all comparisons are available in eTable 7 in Supplement.

Discussion

This network meta-analysis of 90 trials that enrolled 22 028 people living with chronic noncancer pain provides low certainty evidence that cannabis for medical use is similarly effective to opioids for pain relief and sleep quality, and moderate certainty evidence for similar effects on physical functioning. The magnitude of effects vs. placebo for cannabis for medical use or opioids was modest, with the modelled RD for achieving the MID for pain, function and sleep ranging from 5% to 15%. Moderate certainty evidence also suggests that use of cannabis for medical use vs. opioids resulted in fewer discontinuations due to adverse events. Moderate to high certainty evidence showed that neither opioids nor cannabis for medical use were effective for improving emotional, social or role functioning among people living with chronic pain.

Our study, which is the first network meta-analysis exploring the comparative effectiveness of cannabis for medical use and opioids for chronic noncancer pain, has several strengths. We conducted a comprehensive search strategy, including grey literature from clinicaltrials.gov, used the GRADE approach to appraise the certainty of evidence for treatment effects and followed GRADE guidance for communicate our findings. We evaluated harms using discontinuations due to adverse events to facilitate pooling across trials. Further, we explored subgroup effects and assessed their credibility according to current best practices.

Clinical guidelines for chronic noncancer pain recommend optimization of nonopioid based pharmacologic and non-pharmacologic therapies prior to initiating opioids [127-129]. However, approximately a third of all patients living with chronic noncancer pain are prescribed opioids

[130]; and increasing concerns regarding harms of long-term opioid therapy has generated enthusiasm for alternatives, including cannabis for medical use [131]. In part, because some observational studies (but not others [132,133]) have shown an association between legalization of cannabis for medical use and reduced prevalence of opioid use disorder and opioid overdose [134,135]. Although prone to measured and unmeasured confounding bias, recent observational studies and studies using registry data have also shown favourable improvements in pain and health related quality of life outcomes for cannabis for medical use when compared to opioids [136-139]. Moreover, users of cannabis for medical use acknowledge substitution of prescription medication, particularly opioids, as a common motive [140,141]. This issue is controversial [142], however, and recent guidelines have provided conflicting recommendations regarding the effectiveness of cannabis for medical use for chronic pain and whether use of cannabis reduces opioid consumption [11-13,143]. An important limitation of prior evidence syntheses is the scarcity of trials directly comparing cannabis for medical use against opioids for chronic pain. These treatment options are mostly trialed against placebo, and network meta-analysis can therefore establish comparative effectiveness by virtue of this common compactor. Our findings suggest that both opioids and cannabis for medical use may provide benefits for a minority of chronic pain patients (e.g., compared to placebo, 10-15% of patients experience a 1cm or greater relief in pain on a 10cm scale). However, reviews of patient values and preferences show that people living with chronic pain place high value on the possibility of achieving small but important pain relief [144,145]. Furthermore, cannabis does not cause respiratory depression which can result from opioids consumption and lead to non-fatal or fatal overdose [146].

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3 Future research should directly compare the effectiveness of opioids vs. cannabis for chronic
4 pain, and follow patients sufficiently to inform long-term benefits and harms. Trials should
5 report all outcomes measures of importance to people who live with chronic pain [18,19 ,147].
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7 Randomized trials are also needed to establish opioid-substitution effects of cannabis for chronic
8 pain, and observational studies to inform long-term and infrequent harms of both cannabis for
9 medical use and opioids for chronic pain (e.g., overdose, addiction).
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19 There are some limitations associated with our study. None of the trials eligible for our review
20 explored inhaled cannabis, and our results may not be generalizable to this method of
21 administration. We excluded trials with combination drugs because results may be confounded
22 by the additional drugs. As such, our results may not reflect outcomes where opioids or cannabis
23 are used in combination with other drugs (e.g. tramadol and acetaminophen). The cannabis plant
24 contains over 500 chemical substances and the main cannabinoids included in most RCTs are
25 THC, CBD, or THC/CBD and not the full plant. We pooled different opioids and types of
26 cannabis for medical use that may not be common forms of products used in the real-world;
27 however, subgroup analysis suggests that effects for chronic pain are similar across different
28 opioids and cannabis for medical use products [148,149]. Further, a network meta-analysis found
29 no evidence to support important differences in pain relief, functional improvement,
30 or gastrointestinal adverse events between different types of opioids [148]. In order to facilitate
31 pooling, we reported harms as discontinuations due to adverse events instead of reporting
32 specific adverse events experienced by trial participants. In other meta-analyses of RCTs,
33 cannabis for medical use was associated with greater central nervous system and gastrointestinal
34 adverse events, versus placebo [149,150]. Both opioids and cannabis for medical use can result
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3 in use disorders [151,152] while opioids can also result in fatal and non-fatal overdose; however,
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5 we were unable to construct a network to explore the comparative risk of these important harms
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7 as RCTs are poorly suited to detect rare harms or harms that take a while to manifest. We do not
8
9 feel our analysis suffers from serious intransitivity as the distribution of potential effect
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11 modifiers were well balanced across the included studies [153]. Our results for opioids may be
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13 overestimated due to small study effects from the included RCTs for pain relief, physical
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15 functioning and sleep and for pain relief in the cannabis RCTs.
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Conclusions

In this network meta-analysis of randomized trials of patients with chronic noncancer pain, low to moderate certainty evidence suggests that cannabis for medical use may provide similarly small improvements in pain, physical function, and sleep compared to opioids, and fewer discontinuations due to adverse events.

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3 **Contributors:** HMJ, JWB, BS, ML and JET conceived and designed the study. HMJ, LW, AN
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5 performed the statistical analyses. All authors interpreted the data and could access data included
6 in the study. HMJ, JWB and JET drafted the manuscript. All authors made critical revisions to
7 the article for important intellectual content and gave final approval for the article.
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49 **Transparency:** The lead authors affirm that the manuscript is an honest, accurate, and
50 transparent account of the study being reported; that no important aspects of the study have been
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3 omitted; and that any discrepancies from the study as originally planned (and, if relevant,
4
5 registered) have been explained.
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5 **Figure 1: Study Selection Process for the Systematic Review and Network Meta-Analysis**

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7 **Figure 2: Evidence Network for Network Meta-Analysis Outcomes**

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19 chronic non-cancer pain: a systematic review and network meta-analysis of randomised trials. *Br J
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Figure 1: Study Selection Process for the Systematic Review and Network Meta-Analysis

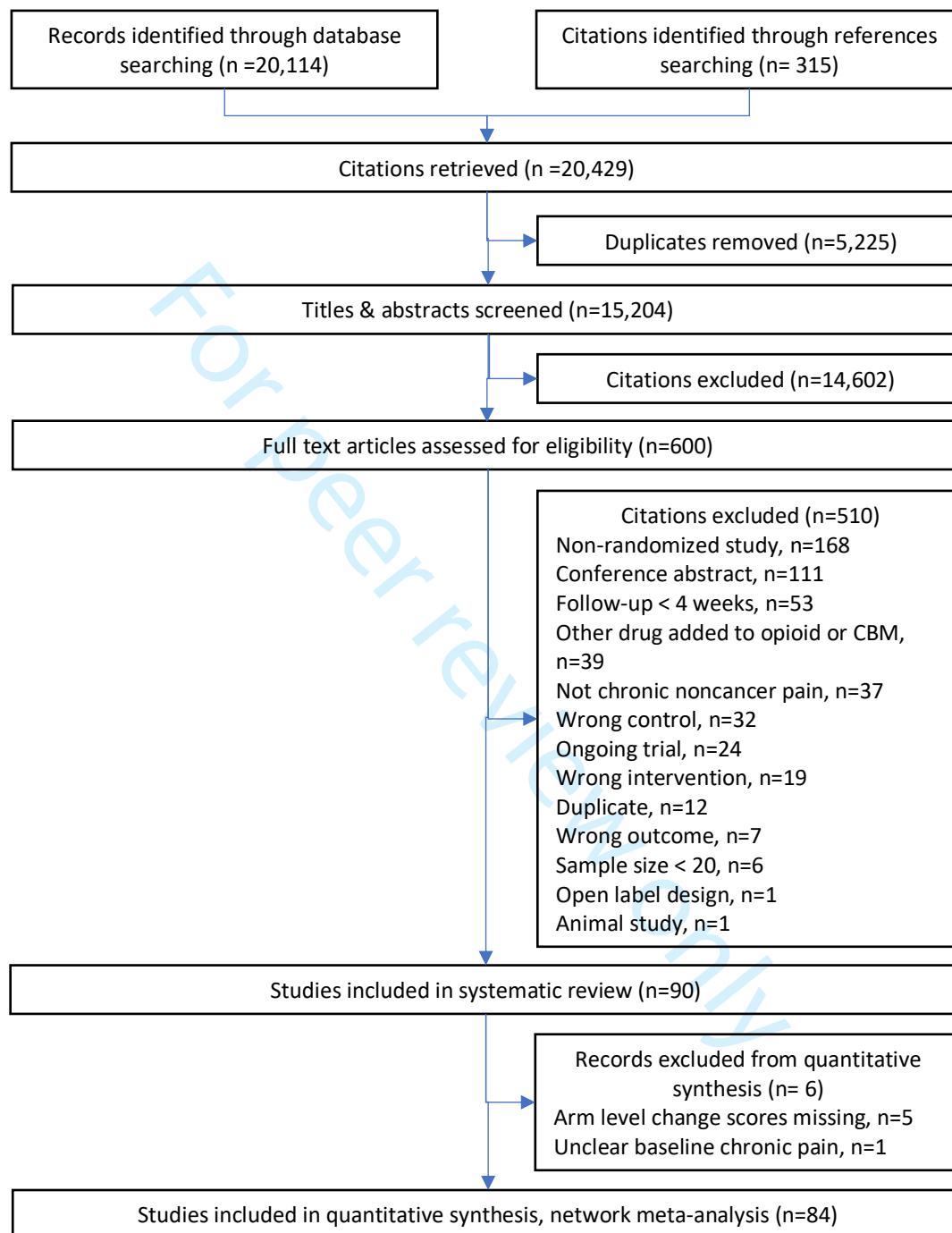
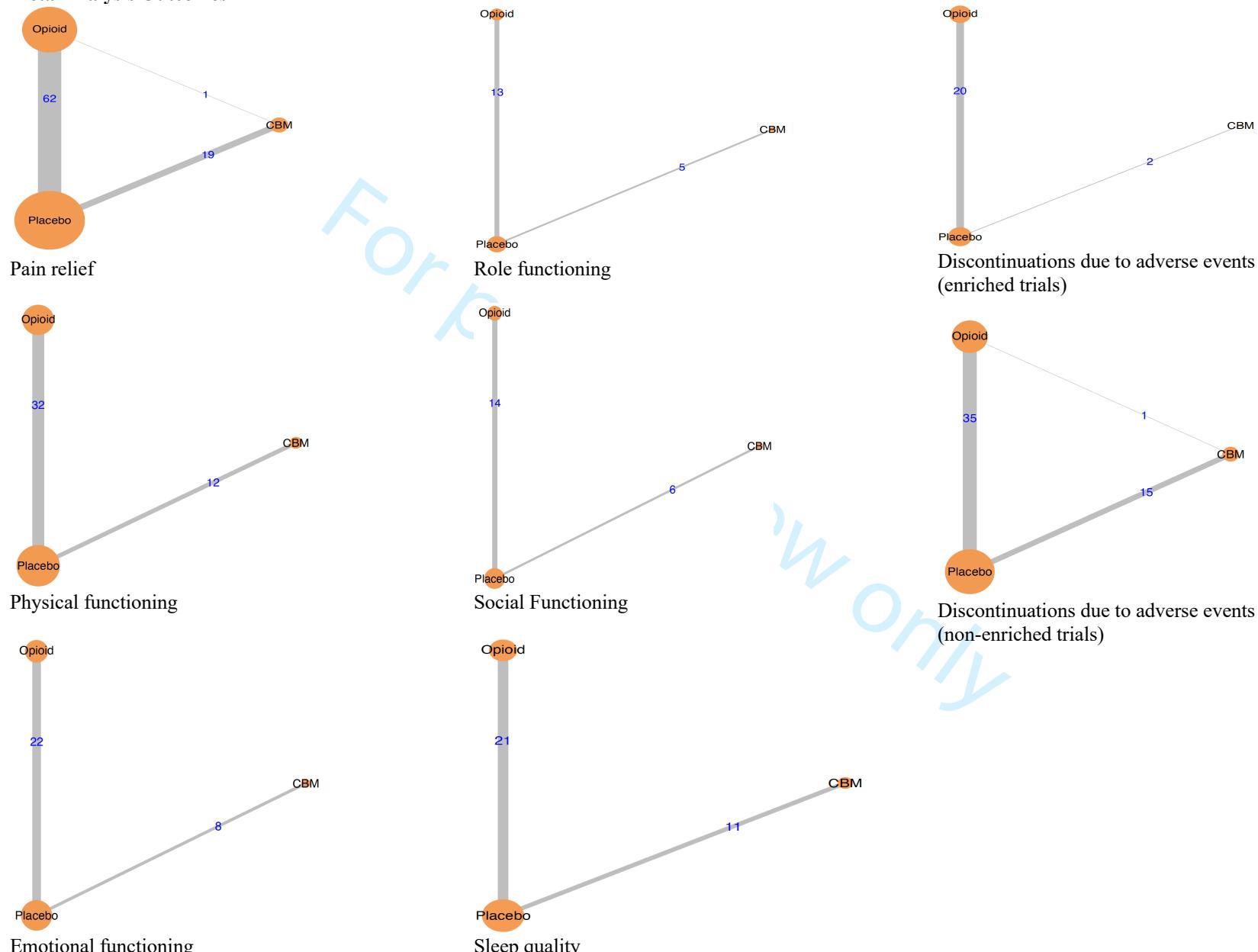


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For peer review only

eAppendix 1: Literature search strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Search Strategy:

1 (chronic adj4 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word,
2 keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique
3 identifier, synonyms] (58120)
4 2 Chronic Pain/ (9487)
5 3 exp Osteoarthritis/ (54546)
6 4 osteoarthrit*.mp. (75997)
7 5 osteo-arthritis.mp. (367)
8 6 degenerative arthrit*.mp. (1219)
9 7 exp Arthritis, Rheumatoid/ (104666)
10 8 exp Neuralgia/ (17706)
11 9 Diabetic Neuropathies/ (13601)
12 10 (neuropath* adj5 (pain* or diabet*)).mp. (36937)
13 11 neuralg*.mp. (23772)
14 12 zoster.mp. (19225)
15 13 Irritable Bowel Syndrome/ (6066)
16 14 (IBS or irritable colon or irritable bowel).mp. (14347)
17 15 Migraine Disorders/ (23014)
18 16 migraine.mp. (34507)
19 17 Fibromyalgia/ (7573)
20 18 fibromyalg*.mp. (10324)
21 19 complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ (5219)
22 20 (complex regional pain syndromes or causalgia).mp. (2139)
23 21 Pain, Intractable/ (6021)
24 22 Phantom Limb/ (1737)
25 23 Hyperalgesia/ (10026)
26 24 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (16519)
27 25 or/1-24 (374187)
28 26 exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ (34838)
29 27 Radiculopathy/ or radiculopathy.mp. (8057)
30 28 musculoskeletal pain/ or headache/ (27891)
31 29 exp Arthralgia/ (10991)
32 30 exp Headache Disorders/ (31166)
33 31 headache*.mp. (83353)
34 32 Temporomandibular Joint Dysfunction Syndrome/ (4838)
35 33 ((TMJ or TMJD) and pain*).mp. (2434)
36 34 whiplash.mp. or exp whiplash injury/ (3756)
37 35 exp Cumulative Trauma Disorders/ (12612)
38 36 exp Peripheral Nervous System Diseases/dt [Drug Therapy] (12959)
39 37 Pain Measurement/de [Drug Effects] (6352)
40 38 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi*
41 or myodyn* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (39779)
42 39 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint*
43 or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or
44 cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (144063)
45 40 or/26-39 (299548)
46 41 (acute or emergency or preoperative or postoperative).ti,ab. (1700816)
47 42 40 not 41 (252546)
48 43 25 or 42 (532409)
49 44 exp Analgesics, Opioid/ (103616)
50 45 (opioid* or opiate*).mp. (114059)
51 46 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or

1
2
3 dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or
4 ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or
5 levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine
6 or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or
7 promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.(143753)
8 47 or/44-46 (199233)
9 48 exp Narcotics/ (111500)
10 49 narcotic*.mp. (57165)
11 50 (adolonta or Anpec or Ardinex or Asimadoline or Alvimapam or amadol or biodalge or biokanol or Codinovo
12 or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or
13 dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or
14 duromorph or duragesic or durogesic or eucodal or Fedotzine or Fenantest or Fentora or Fortral or Hycodan or
15 Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or
16 isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or
17 lexir or lidol or lydol or morfin or morphine or morphin or morphinium or morphinene or morphium or ms
18 contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or
19 oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or
20 skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or
21 tramadolhameln or tramadol or tramadura or tramagetic or tramagit or tramal or tramex or tramundin
22 or trasedal or theradol or tiral or topalge or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin
23 or tramadoc or ultram or zamudol or zumalge or zyadol or zytram).mp. [mp=title, abstract, original title, name of
24 substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease
supplementary concept word, unique identifier, synonyms] (9563)
25 51 or/44-50 (227775)
26 52 43 and 51 (22678)
27 53 epidemiologic studies/ (7641)
28 54 exp Case-Control Studies/ (904344)
29 55 exp Cohort Studies/ (1723417)
30 56 Case control.tw. (106622)
31 57 (cohort adj (study or studies)).tw. (151570)
32 58 Cohort analy\$.tw. (6083)
33 59 (Follow up adj (study or studies)).tw. (44718)
34 60 ((observational or epidemiol*) adj (study or studies)).tw. (156420)
35 61 Longitudinal.tw. (201362)
36 62 Retrospective.mp. or prospective.tw. (1247587)
37 63 Cross sectional.tw. (272577)
38 64 Cross-sectional studies/ (260504)
39 65 or/53-64 (2717825)
40 66 exp animals/ not humans.sh. (4438182)
41 67 65 not 66 (2649950)
42 68 52 and 67 (3763)
43 69 randomized controlled trial.pt. (456617)
44 70 controlled clinical trial.pt. (92277)
45 71 randomized.ab. (406479)
46 72 placebo.ab. (187496)
47 73 drug therapy.fs. (2003496)
48 74 randomly.ab. (287373)
49 75 trial.ab. (422125)
50 76 groups.ab. (1777409)
51 77 or/69-76 (4167722)
52 78 clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs. (5199787)
53 79 randomized controlled trial.pt. or randomized controlled trial.mp. (476635)
54 80 randomized controlled trial.pt. or randomized.mp. or placebo.mp. (790362)
55 81 or/78-80 (5214838)
56 82 77 or 81 (6680171)
57 83 exp animals/ not humans.sh. (4438182)

1
2
3 84 82 not 83 (5604099)
4 85 43 and 51 and 84 (14496)
5 86 limit 85 to yr="2010 -Current" (6438)
6 87 68 or 86 (8377)
7 88 (MEDLINE or systematic review or literature search).tw. or meta analysis.mp,pt. (256038)
8 89 43 and 51 and 88 (881)
9 90 87 or 89 (8697)
10 91 exp Sleep Apnea Syndromes/ (30607)
11 92 sleep apn?ea.mp. (38637)
12 93 sleep-disordered breathing.mp. (5685)
13 94 hypogonadism.mp. or Hypogonadism/ (13040)
14 95 ((testosterone or androgen) and (deprivation or deficiency)).mp. (12336)
15 96 OPIAD.mp. (10)
16 97 or/91-96 (64161)
17 98 52 and 97 (144)
18 99 90 or 98 (8736)

19 **PsycInfo**

20 **Database: PsycINFO via OVID**

21 Search Strategy:

22 1 (chronic adj4 pain*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests &
23 measures] (19944)
24 2 chronic pain/ (12078)
25 3 exp arthritis/ (3853)
26 4 osteoarthrit*.mp. (1758)
27 5 osteo-arthritis.mp. (8)
28 6 degenerative arthrit*.mp. (15)
29 7 exp neuralgia/ (892)
30 8 exp neuropathy/ (5931)
31 9 (neuropath* adj5 (pain* or diabet*)).mp. (6256)
32 10 neuralg*.mp. (1530)
33 11 zoster.mp. (550)
34 12 irritable bowel syndrome/ (1055)
35 13 (IBS or irritable colon or irritable bowel).mp. [mp=title, abstract, heading word, table of contents, key
36 concepts, original title, tests & measures] (1832)
37 14 migraine headache/ (8772)
38 15 migraine.mp. (11715)
39 16 fibromyalgia/ (1768)
40 17 fibromyalg*.mp. (3042)
41 18 complex regional pain syndromes.mp. (55)
42 19 "complex regional pain syndrome (type i)"/ (137)
43 20 (complex regional pain syndromes or causalgia).mp. (109)
44 21 somatosensory disorders/ (1266)
45 22 hyperalgesi*.mp. (3914)
46 23 somatoform pain disorder/ (801)
47 24 somatoform disorders/ (7528)
48 25 conversion disorder/ (998)
49 26 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (3008)
50 27 or/1-26 (58879)
51 28 back pain.mp. or exp Back Pain/ (5353)
52 29 radiculopathy.mp. (202)
53 30 musculoskeletal pain.mp. (1410)
54 31 Arthralgia.mp. (105)
55 32 headache.mp. or exp HEADACHE/ (19164)
56 33 ((TMJ or TMJD) and pain*).mp. (142)
57 34 WHIPLASH/ or whiplash.mp. (571)

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3 35 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi*
4 or myodyn* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (5452)
5 36 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint*
6 or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or
7 cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (18302)
8 37 or/28-36 (39808)
9 38 (acute or emergency or preoperative or postoperative).ti,ab. (111436)
10 39 37 not 38 (35095)
11 40 27 or 39 (71492)
12 41 exp opiates/ (22978)
13 42 (opioid* or opiate*).mp. (27750)
14 43 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or
15 dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or
16 ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or
17 levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine
18 or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or
19 promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (27830)
20 44 exp narcotic drugs/ (27031)
21 45 narcotic*.mp. (5729)
22 46 (adolonta or Anpec or Ardinex or Asimadoline or Alvimapam or amadol or biodaligic or biokanol or Codinovo
23 or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or
24 dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or
25 duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or
26 Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or
27 isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or
28 lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms
29 contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or
30 oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or
31 skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or
32 tramadolhameln or tramadol or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin
33 or trasedal or theradol or tiral or topalgeic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin
34 or tramadoc or ultram or zamudol or zumalgec or zydol or zytram).mp. (928)
35 47 or/41-46 (47945)
36 48 37 and 47 (2028)
37 49 animals/ not humans/ (7067)
38 50 animal models/ (29760)
39 51 animal research/ (368)
40 52 exp rodents/ (201732)
41 53 (rat or rats or mouse or mice).ti. (110418)
42 54 or/49-53 (226624)
43 55 48 not 54 (1547)

Database: AMED (Allied and Complementary Medicine) via OVID

Search Strategy:

1 analgesics opioid/ (335)
2 (opioid* or opiate*).mp. (1449)
3 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or
4 dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or
5 ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or
6 levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine
7 or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or
8 promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. [mp=abstract, heading words,
title] (1097)
9 4 narcotics/ (177)
10 5 narcotic*.mp. (345)
11 6 (adolonta or Anpec or Ardinex or Asimadoline or Alvimapam or amadol or biodaligic or biokanol or Codinovo

1
2
3 or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or
4 dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or
5 duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or
6 Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or
7 isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or
8 lexit or lidol or lydol or morfin or morphia or morphin or morphinium or morphinene or morphium or ms
9 contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or
10 oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or
11 skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or
12 tramadolhameln or tramadol or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin
13 or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin
14 or tramadoc or ultram or zamudol or zumalgie or zydol or zytram).mp. [mp=abstract, heading words, title] (109)
15 7 or/1-6 (2268)
16 8 (chronic adj4 pain).mp. [mp=abstract, heading words, title] (4640)
17 9 exp arthritis/ (5636)
18 10 arthralgia/ (189)
19 11 fibromyalgia/ (1656)
20 12 neuralgia/ (157)
21 13 diabetic neuropathies/ (264)
22 14 (neuropath* adj5 (pain* or diabet*)).mp. (981)
23 15 neuralg*.mp. [mp=abstract, heading words, title] (335)
24 16 osteoarthrit*.mp. [mp=abstract, heading words, title] (3321)
25 17 irritable bowel syndrome/ (133)
26 18 (IBS or irritable colon or irritable bowel).mp. [mp=abstract, heading words, title] (297)
27 19 fibromyalg*.mp. [mp=abstract, heading words, title] (1846)
28 20 Migraine/ or migraine.mp. (651)
29 21 complex regional pain syndromes/ or reflex sympathetic dystrophy/ (188)
30 22 (complex regional pain syndromes or causalgia).mp. [mp=abstract, heading words, title] (77)
31 23 pain intractable/ (431)
32 24 hyperalgesia/ or phantom limb/ (181)
33 25 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. [mp=abstract,
34 heading words, title] (675)
35 26 or/8-25 (15230)
36 27 exp backache/ (6186)
37 28 radiculopathy.mp. (290)
38 29 exp Headache/ or headache.mp. (1709)
39 30 Temporomandibular joint syndrome/ (67)
40 31 ((TMJ or TMJD) and pain*).mp. (28)
41 32 Whiplash injuries/ or whiplash.mp. (594)
42 33 repetition strain injury/ (312)
43 34 (backache* or backpain* or dorsalmgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi*
44 or myodyn* or neuralg* or ischialg* or crps or rachialg*).ab,ti. (2429)
45 35 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint*
46 or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or
47 cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (12871)
48 36 or/27-35 (17684)
49 37 (acute or emergency or preoperative or postoperative).ti,ab. (12782)
50 38 36 not 37 (16319)
51 39 26 or 38 (25280)
52 40 7 and 39 (532)
53 41 (rat or rats or mouse or mice).ti. (5925)
54 42 animals/ not humans/ (7083)
55 43 exp Rodents/ (8142)
56 44 41 or 42 or 43 (10161)
57 45 40 not 44 (512)
58 Central (Cochrane Library via Wiley)
59
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1
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3 Description:
4 ID Search Hits
5 #1 chronic near/3 pain 9973
6 #2 MeSH descriptor: [Chronic Pain] explode all trees 1178
7 #3 MeSH descriptor: [Osteoarthritis] explode all trees 4754
8 #4 osteoarthrit* 10561
9 #5 osteo-arthritis 69
10 #6 degenerative arthrit* 359
11 #7 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees 4858
12 #8 MeSH descriptor: [Neuralgia] explode all trees 1049
13 #9 MeSH descriptor: [Diabetic Neuropathies] explode all trees 1397
14 #10 neuropath* near/5 (pain* or diabet*) 4465
15 #11 neuralg* 1913
16 #12 zoster 1641
17 #13 MeSH descriptor: [Irritable Bowel Syndrome] explode all trees 674
18 #14 irritable (colon or bowel) 2448
19 #15 IBS 1629
20 #16 MeSH descriptor: [Migraine Disorders] explode all trees 1959
21 #17 migraine 4659
22 #18 MeSH descriptor: [Fibromyalgia] explode all trees 851
23 #19 fibromyalg* 1987
24 #20 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees 238
25 #21 complex regional pain syndromes or causalgia 203
26 #22 MeSH descriptor: [Pain, Intractable] explode all trees 273
27 #23 MeSH descriptor: [Phantom Limb] explode all trees 75
28 #24 MeSH descriptor: [Hyperalgesia] explode all trees 454
29 #25 ((noncancer* or non-cancer* or chronic* or recurrent or persist* or non-malign*) near/3 pain) 2107
30 #26 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 40797
31 #27 MeSH descriptor: [Back Pain] explode all trees 3879
32 #28 MeSH descriptor: [Radiculopathy] explode all trees 303
33 #29 MeSH descriptor: [Musculoskeletal Pain] explode all trees 478
34 #30 MeSH descriptor: [Arthralgia] explode all trees 1313
35 #31 MeSH descriptor: [Headache Disorders] explode all trees 2415
36 #32 MeSH descriptor: [Headache] explode all trees 1798
37 #33 headache* 26942
38 #34 MeSH descriptor: [Temporomandibular Joint Dysfunction Syndrome] explode all trees 179
39 #35 ((TMJ or TMJD) and pain*) 266
40 #36 MeSH descriptor: [Whiplash Injuries] explode all trees 208
41 #37 whiplash 460
42 #38 MeSH descriptor: [Cumulative Trauma Disorders] explode all trees 668
43 #39 backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or
fibromyalgi* or myodyn* or neuralgi* or ischialgi* or crps or rachialgi* 13481
44 #40 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or
joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or
cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) near/3 pain) 28955
45 #41 radiculopathy 893
46 #42 #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41
60275
47 #43 acute or emergency or preoperative or postoperative 200646
48 #44 42 not 43 59058
49 #45 #26 or #44 97623
50 #46 opioid* or opiate* 17932
51 #47 narcotic* 6752
52 #48 MeSH descriptor: [Analgesics, Opioid] explode all trees 6462
53 #49 MeSH descriptor: [Narcotics] explode all trees 7246
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#50 alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphone or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol 32420
#51 adolonta or Anpec or Ardinex or Asimadoline or Alvimapam or amadol or biodaligic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydronal or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramacetic or tramagit or tramake or tramal or tramex or tramundin or trasadal or theradol or tiral or topalgc or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgc or zydot or zytram 5622
#52 #46 or #47 or #48 or #49 or #50 or #51 42294
#53 #45 and #52 2656

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Search Strategy:

-
- 1 Cannabis/ (11443)
 - 2 exp cannabinoids/ or cannabidiol/ or cannabinol/ or dronabinol/ (16399)
 - 3 Endocannabinoids/ (6489)
 - 4 exp Receptors, Cannabinoid/ (10396)
 - 5 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*).mp. (64927)
 - 6 or/1-5 (64927)
 - 7 pain*.mp.jw. or Pain/ (890667)
 - 8 exp Osteoarthritis/ or exp Arthritis, Rheumatoid/ or exp Neuralgia/ or Diabetic Neuropathies/ or Irritable Bowel Syndrome/ or Migraine Disorders/ or Fibromyalgia/ or complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ or Pain, Intractable/ or chronic pain/ or Phantom Limb/ or Hyperalgesia/ or exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ or Radiculopathy/ or musculoskeletal pain/ or headache/ or exp Arthralgia/ or exp Headache Disorders/ or Temporomandibular Joint Dysfunction Syndrome/ or exp whiplash injury/ or exp Cumulative Trauma Disorders/ or exp Peripheral Nervous System Diseases/dt or Pain Measurement/de (423216)
 - 9 ((irrita* or inflam*) adj4 (bowel or colon)).mp. (81237)
 - 10 (osteoartrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*).mp. (827784)
 - 11 Muscle Spasticity/ (9871)
 - 12 Muscle Hypertonia/ (1033)
 - 13 (spasticity or spasm or spastic or hypertonia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (56343)
 - 14 or/7-13 (1660232)

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3 15 6 and 14 (6752)
4 16 random:.tw. or placebo:.mp. or double-blind:.tw. (1409704)
5 17 ((treatment or control) adj3 group*).ab. (680082)
6 18 (allocat* adj5 group*).ab. (29935)
7 19 ((clinical or control*) adj3 trial).ti,ab,kw. (333663)
8 20 or/16-19 (1961120)
9 21 randomized controlled trial.pt. (561669)
10 22 controlled clinical trial.pt. (94744)
11 23 clinical trials as topic.sh. (199529)
12 24 randomly.ab. (378041)
13 25 trial.ti. (258476)
14 26 drug therapy.fs. (2458509)
15 27 or/16-26 (4232754)
16 28 15 and 27 (3200)
17 29 animals/ not humans/ (4940789)
18 30 28 not 29 (2513)

EMBASE (OVID)

Search Strategy:

1 cannabis/ (39161)
2 exp cannabinoid/ (76903)
3 medical cannabis/ (3242)
4 exp cannabinoid receptor/ (16300)
5 exp endocannabinoid/ (10122)
6 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetrabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (101727)
7 or/1-6 (103167)
8 pain/ or pain*.mp. (1523452)
9 chronic pain/ or exp osteoarthritis/ or exp rheumatoid arthritis/ or exp neuralgia/ or diabetic neuropathy/ or irritable colon/ or exp migraine/ or fibromyalgia/ or intractable pain/ or agnosia/ or exp radiculopathy/ or musculoskeletal pain/ or exp arthralgia/ or headache/ or temporomandibular joint disorder/ or whiplash injury/ or exp cumulative trauma disorder/ (947642)
10 (osteoartrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (1588678)
11 ((irrita* or inflam*) adj4 (bowel or colon)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (143101)
12 muscle hypertonia/ or spasticity/ (29975)
13 (spasticity or spasm or spastic or hypertonia).mp. (102572)
14 or/8-13 (2856349)
15 7 and 14 (15652)
16 clinical article/ (2840832)
17 exp clinical study/ (11038373)
18 clinical trial/ (1030530)
19 controlled study/ (8707614)
20 randomized controlled trial/ (700351)

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2
3 21 major clinical study/ (4407914)
4 22 double blind procedure/ (193251)
5 23 multicenter study/ (318443)
6 24 single blind procedure/ (45524)
7 25 phase 3 clinical trial/ (59538)
8 26 phase 4 clinical trial/ (4691)
9 27 crossover procedure/ (69709)
10 28 placebo/ (378215)
11 29 or/16-28 (15939371)
12 30 allocat\$.mp. (195320)
13 31 assign\$.mp. (446472)
14 32 blind\$.mp. (548005)
15 33 (clinic\$ adj25 (study or trial)).mp. (7617865)
16 34 compar\$.mp. (9098845)
17 35 control\$.mp. (12329430)
18 36 cross?over.mp. (108597)
19 37 factorial\$.mp. (69675)
20 38 follow?up.mp. (50719)
21 39 placebo\$.mp. (491115)
22 40 prospectiv\$.mp. (1372469)
23 41 random\$.mp. (2010437)
24 42 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).mp. (348231)
25 43 trial.mp. (2377246)
26 44 (versus or vs).mp. (2518554)
27 45 or/30-44 (19623398)
28 46 29 and 45 (12865583)
29 47 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or
30 nonhuman/ (30266244)
31 48 human/ or normal human/ or human cell/ (23473918)
32 49 47 and 48 (23405621)
33 50 47 not 49 (6860623)
34 51 46 not 50 (10162086)
35 52 randomized controlled trial.pt. or randomi?ed.mp. or placebo.mp. (1559060)
36 53 ((treatment or control) adj3 group*).ab. (985064)
37 54 (allocat* adj5 group*).ab. (39102)
38 55 ((clinical or control*) adj3 trial).ti,ab,kw. (472392)
39 56 52 or 53 or 54 or 55 (2453456)
40 57 15 and 51 (5650)
41 58 15 and 56 (2581)
42 59 57 or 58 (6324)

43 **AMED (OVID)**

44 **Database: AMED (Allied and Complementary Medicine)**

45 Search Strategy:

46 1 exp cannabis/ (250)
47 2 cannabinoids/ (59)
48 3 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or
49 hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or
50 cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or
51 nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or
52 sativex or endocannabinoid*).mp. [mp=abstract, heading words, title] (434)
53 4 or/1-3 (434)
54 5 pain.mp. or Pain/ (35918)
55 6 exp arthritis rheumatoid/ or exp osteoarthritis/ (5358)
56 7 exp pain/ or neuralgia/ (23893)

1
2
3 8 exp diabetic neuropathies/ (1040)
4 9 irritable bowel syndrome/ (199)
5 10 Migraine/ (513)
6 11 fibromyalgia/ or myofascial pain syndromes/ or temporomandibular joint syndrome/ (2280)
7 12 complex regional pain syndromes/ or reflex sympathetic dystrophy/ (197)
8 13 Phantom limb/ (134)
9 14 hyperalgesia/ (74)
10 15 whiplash injuries/ (546)
11 16 repetition strain injury/ (324)
12 17 (osteoarthritis* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or
13 fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalg* or arthralgi* or
14 polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or
15 crohn* or colitis* or enteritis* or ileitis*).mp. (18652)
16 18 ((irrita* or inflam*) adj4 (bowel or colon)).mp. (585)
17 19 Muscle spasticity/ (1183)
18 20 Muscle hypertonia/ (84)
19 21 (spasticity or spasm or spastic or hypertonia).mp. [mp=abstract, heading words, title] (2678)
20 22 or/5-21 (50501)
21 23 4 and 22 (118)

22
23 **PsycInfo (OVID)**

24 **Database: APA PsycInfo**

25 Search Strategy:

26
27 1 exp cannabis/ or exp cannabinoids/ or tetrahydrocannabinol/ (15070)
28 2 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or
29 hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or
30 cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or
31 nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetrabinex or
32 sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title,
33 tests & measures, mesh word] (30531)
34 3 1 or 2 (30531)
35 4 pain*.mp. or exp PAIN/ (140896)
36 5 (osteoarthritis* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or
37 fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalg* or arthralgi* or
38 polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or
39 crohn* or colitis* or enteritis* or ileitis*).mp. [mp=title, abstract, heading word, table of contents, key concepts,
40 original title, tests & measures, mesh word] (74571)
41 6 4 or 5 (180976)
42 7 3 and 6 (2094)
43 8 limit 7 to "therapy (best balance of sensitivity and specificity)" (372)
44 9 (double-blind or random: assigned or control).tw. (522132)
45 10 clinical trials/ (12034)
46 11 (controlled adj3 trial*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title,
47 tests & measures, mesh word] (58491)
48 12 (clinical adj2 trial*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests
49 & measures, mesh word] (50934)
50 13 (randomi?ed adj7 trial*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title,
51 tests & measures, mesh word] (69435)
52 14 or/9-13 (589510)
53 15 7 and 14 (525)
54 16 8 or 15 (525)
55 17 muscle spasms/ (522)
56 18 (spasticity or spasm or spastic or hypertonia).mp. [mp=title, abstract, heading word, table of contents, key
57 concepts, original title, tests & measures, mesh word] (5660)

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3 19 17 or 18 (5767)
4 20 3 and 19 (129)
5 21 limit 20 to "therapy (best balance of sensitivity and specificity)" (36)
6 22 14 and 20 (80)
7 23 21 or 22 (80)
8 24 16 or 23 (548)
9
10 Cochrane Library (Wiley)

11 ID Search Hits
12 #1 MeSH descriptor: [Cannabis] 1 tree(s) exploded 10
13 #2 MeSH descriptor: [Cannabinoids] explode all trees 928
14 #3 MeSH descriptor: [Endocannabinoids] explode all trees 63
15 #4 MeSH descriptor: [Endocannabinoids] explode all trees 63
16 #5 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah
17 or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or
18 cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or
19 nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or
20 sativex or endocannabinoid*):ti,ab,kw (Word variations have been searched) 5386
21 #6 #1 or #2 or #3 or #4 or #5 5386
22 #7 MeSH descriptor: [Pain] explode all trees 54054
23 #8 (pain*):ti,ab,kw (Word variations have been searched) 207177
24 #9 #7 or #8 213544
25 #10 #6 and #9 794
26 #11 [mh Osteoarthritis] or [mh ^"Arthritis, Rheumatoid"] or [mh Neuralgia] or [mh ^"Diabetic Neuropathies"]
27 or [mh ^"Irritable Bowel Syndrome"] or [mh ^"Migraine Disorders"] or [mh Fibromyalgia] or [mh ^"complex
28 regional pain syndromes"] or [mh causalgia] or [mh ^"reflex sympathetic dystrophy"] or [mh ^"pain Intractable"] or
29 [mh ^"Phantom Limb"] or [mh Hyperalgesia] or [mh ^"back pain"] or [mh ^"failed back surgery syndrome"] or [mh
30 ^"low back pain"] or [mh Radiculopathy] or [mh ^"musculoskeletal pain"] or [mh headache] or [mh Arthralgia] or
31 [mh ^"Headache Disorders"] or [mh ^"Temporomandibular Joint Dysfunction Syndrome"] or [mh ^"whiplash
32 injury"] or [mh ^"Cumulative Trauma Disorders"] or [mh "Peripheral Nervous System Diseases"/DT] or [mh ^"Pain
33 Measurement"/DE] 35211
34 #12 (osteoarthrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache*
35 or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or
36 polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or
37 crohn* or colitis* or enteritis* or ileitis*) 126119
38 #13 (irrita* or inflam*) near/4 (bowel or colon) 8688
39 #14 #11 or #12 or #13136956
40 #15 #6 and #14 513
41 #16 #10 or #15 in Trials 909
42 #17 MeSH descriptor: [Muscle Spasticity] explode all trees 999
43 #18 MeSH descriptor: [Muscle Hypertonia] explode all trees 1118
44 #19 spasticity or spasm or spastic or hypertonia 8777
45 #20 #17 or #18 or #198841
46 #21 #20 and #6 198
47 #22 #10 or #15 or #21 in Trials1001
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54 CINAHL (EBSCO)
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#	Query	Results
S51	S49 OR S50	849
S50	S48	427
S49	S29 AND S48	721
S48	S4 AND S47	2,847
S47	S7 OR S36 OR S46	580,420
S46	S43 OR S44 OR S45	14,915
S45	TX spasticity or spasm or spastic or hypertonia (MH "Muscle Hypertonia")	14,915
S44	(MH "Muscle Spasticity")	517
S43	S31 OR S41	802
S42	S39 OR S40	169
S41	S29 AND S38	154
S40	S38	49
S39	S37 NOT S8	464
S38	S4 AND S36	2,025
S37	S32 OR S33 OR S34 OR S35	458,156
S36	(irrita* or inflam*) N4 (bowel or colon)	18,662
S35	TX (osteoarthritis* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*)	269,583
S34	(MH Pain+) OR (MH Phantom Limb) OR (MH Hyperalgesia) OR (MH back pain+) OR (MH "failed back surgery syndrome+") OR (MH "low back pain+") OR (MH Radiculopathy) OR (MH "musculoskeletal pain") OR (MH headache) OR (MH Arthralgia+) OR (MH "Headache Disorders+") OR (MH "Temporomandibular Joint Dysfunction Syndrome") OR (MH "whiplash injury+/" OR (MH "Cumulative Trauma Disorders+"))	226,279
S33	TX (MH Osteoarthritis+) OR (MH "Arthritis, Rheumatoid+") OR (MH Neuralgia) OR (MH Diabetic Neuropathies) OR (MH "Irritable Bowel Syndrome") OR (MH "Migraine Disorders") OR (MH Fibromyalgia) OR (MH "complex regional pain syndromes") OR (MH causalgia+) OR (MH "reflex sympathetic dystrophy+")	85,767
S32	S9 OR S30	633

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3	S30	S8 AND S29	526
4	S29	S16 OR S21 OR S28	1,384,715
5	S28	S22 OR S23 OR S24 OR S25 OR S26 OR S27	1,181,925
6	S27	(MH "Prospective Studies+")	495,834
7	S26	(MH "Evaluation Research+")	330,364
8	S25	(MH "Comparative Studies")	426,809
9	S24	"latin square"	248
10	S23	(MH "Study Design") OR (MH "Crossover Design") OR (MH "Experimental Studies+")	423,651
11	S22	(MH "Random Sample+")	116,667
12	S21	S17 OR S18 OR S19 OR S20	493,219
13	S20	"random*"	475,828
14	S19	"placebo*"	73,590
15	S18	(MH "Placebos")	13,285
16	S17	(MH "Placebo Effect")	2,426
17	S16	S10 OR S11 OR S12 OR S13 OR S14 OR S15	455,728
18	S15	"triple-blind"	489
19	S14	"single-blind"	17,122
20	S13	"double-blind"	63,811
21	S12	clinical W3 trial	278,173
22	S11	"randomi?ed controlled trial*"	200,563
23	S10	(MH "Clinical Trials+")	333,661
24	S9	S4 AND S7	344
25	S8	S4 AND S7	2,279
26	S7	S5 OR S6	364,720
27	S6	"pain"	342,481
28	S5	(MH "Pain+")	223,572
29	S4	S1 OR S2 OR S3	24,367
30	S3	Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or	24,367
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	tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetrabinex or sativex or endocannabinoid*	
S2	(MH "Medical Marijuana")	2,127
S1	(MH "Cannabis")	10,569

PubMed

Search: (((((((((pain* OR spasticity OR spasm OR spastic OR hypertonia OR osteoarthrit* OR osteo-arthritis OR arthrit* OR neuropath* OR neuralgi* OR zoster* OR migraine* OR headache* OR fibromyalgi* OR causalgia OR radiculopathy* OR whiplash OR backache* OR backpain* OR dorsalgi* OR arthralgi* OR polyarthralgi* OR arthrodyni* OR myalgi* OR myodyn* OR ischialgi* OR crps OR brachialgia *or tmj OR tmjd OR IBS OR crohn* OR colitis* OR enteritis* OR ileitis*)) AND ((trial* OR random*))) AND ((cannabis OR cannabinol OR cannabinoid* OR cannabidiol OR bhang OR hashish OR hemp OR marihuana OR marijuana OR nabilone OR cesamet OR tetrahydrocannabinol OR dronabinol OR levonantradol OR nabiximols OR palmidrol OR tetrahydrocannabinolic OR sativex OR endocannabinoid*)))) AND ((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))) Sort by: Most Recent

Web of Science

10 #8 AND #9 1,871
9 TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*) 5,772,934
8 #7 AND #1 7,146
7 #6 OR #5 OR #4 OR #3 OR #2 1,648,139
6 TS=(spasticity or spasm or spastic or hypertonia) 50,631
5 TS= tmj OR TS= tmjd OR TS= IBS OR TS= crohn* OR TS= colitis* OR TS= enteritis* OR TS= ileitis* 185,102
4 TS= arthrodyni* OR TS= myalgi* OR TS= myodyn* OR TS= ischialgi* OR TS= crps OR TS= brachialgia 13,911
3 TS= headache* OR TS=fibromyalgi* OR TS= causalgia OR TS= radiculopathy* OR TS= whiplash OR TS= backache* OR TS= backpain* OR TS= dorsalgi* OR TS= arthralgi* OR TS= polyarthralgi* 129,034
2 TS= pain* OR TS=osteoarthrit* OR TS= osteo-arthritis OR TS= arthrit* OR TS=neuropath* OR TS= neuralgi* OR TS=zoster* OR TS= migraine* 1,373,602
1 TS=cannabis OR TS= cannabinol OR TS= cannabinoid* OR TS=cannabidiol OR TS=bhang OR TS=hashish OR TS= hemp OR TS=marihuana OR TS= marijuana OR TS= nabilone OR TS= cesamet OR TS= tetrahydrocannabinol OR TS= dronabinol OR TS= levonantradol OR TS= nabiximols OR TS= palmidrol OR TS=tetrahydrocannabinolic OR TS=sativex OR TS= endocannabinoid* 82,113

Cannabis-Med

International Association for Cannabinoid Medicines, database of clinical studies

<http://www.cannabis-med.org/studies/study.php>

Diagnosis: Pain or spasticity

AND

Study design: Controlled Study

Cannabinoids for chronic non-cancer pain (matrix of evidence)

<https://www.epistemonikos.org/en/matrixes/58f5158d7aac87666ca8853>

97 Primary Studies

Cannabis Spasticity

45 Primary studies

eAppendix 2: Full reference list of eligible studies

(Studies reported 2 separate trials in one paper: Arai et al. 2015, and Tominaga et al 2016.)

1. Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig* 2010;30(8):489-505. doi: 10.2165/11533440-000000000-00000.
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eAppendix 3: Reference list of studies excluded from quantitative analysis

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eTable 1. Psychometric studies for instruments used for measuring patient reported outcomes in eligible randomized controlled trials

Outcome	Instruments and psychometric studies
Pain relief	4-point categorical scale ¹ ; 5 point Likert scale ² ; Brief Pain Inventory ^{3,4} ; Multidimensional pain inventory (MPI-S) swedish version ⁵ ; Neuropathic Pain Scale ^{6,7} ; Short-form McGill Pain Questionnaire ³ ; Visual pain intensity scale ³ ; WOMAC Pain subscale ^{3,8}
Physical functioning	Back pain functional scale ⁹ ; Barthel index; BPI walking ability subscale ^{3,4} ; Disability Assessment Scale; Guy's Neurological Disability Scale (GNDS) ¹⁰ ; Oswestry Disability Index ^{11,12} ; Pain Disability Index ¹³ ; Roland Morris Disability Questionnaire ^{13,14} ; SF-12 PCS ¹⁵ ; Shortened Treatment Outcomes in Pain Survey instrument (S-TOPS) ¹⁶ ; WOMAC PF scale ^{3,8}
Emotional functioning	BPI mood subscale ^{3,4} ; General Health Questionnaire (GHQ-30); Profile of Mood states ³ ; VAS Bond and Lader mood ¹⁷
Role functioning	Pain Disability Index ¹³ ; S-TOPS Role-emotional disability ¹⁶
Social functioning	BPI relations with other people subscale ^{3,4} ; S-TOPS Family-social disability ¹⁶
Sleep quality	BPI sleep ^{3,4} ; Medical Outcomes Study Sleep Scale ¹⁸

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eTable 2. Baseline characteristics of eligible randomized controlled trials (N = 90 RCTs)

Author	Total # randomized	Pain condition	Age (year)	Sex (female%)	Duration of chronic pain(month)	# of arms	Interventions	Control	Length of follow-up (days)
Opioids versus placebo									
Afilalo (2010)	1030	Osteoarthritis	58	61	NR	3	Tapentadol-ER Oxycodone-ER	Placebo	84
Arai (2015)	150	Mixed neuropathic & non-neuropathic conditions	66	67	NR	2	Fentanyl-PATCH	Placebo	84
Arai (2015)	163	Mixed neuropathic	66	49	NR	2	Fentanyl-PATCH	Placebo	84
Babul (2004)	246	Osteoarthritis	61	61	154	2	Tramadol-ER	Placebo	84
Boureau (2003)	127	Postherpetic neuralgia	66	62	6.7	2	Tramadol-ER	Placebo	42
Breivik (2010)	199	Osteoarthritis	50	58	NR	2	Buprenorphine-PATCH	Placebo	180
Burch (2007)	646	Osteoarthritis	62	63	NR	2	Tramadol-ER	Placebo	84
Buynak (2010)	981	Low back pain	50	58	NR	3	Tapentadol-ER; Oxycodone-ER	Placebo	105
Caldwell (2002)	295	Osteoarthritis	61	62	NR	4	Morphine-ER	Placebo	28
Caldwell (1999)	70	Osteoarthritis	57	53	NR	3	Oxycodone-ER	Placebo	28
Christoph (2017)	252	neuropathic & non-neuropathic conditions		62	NR	5	Tapentadol-ER	Placebo	98
Chu (2012)	139	Low back pain	45	44	NR	2	Morphine-ER	Placebo	30
DeLemos (2011)	808	Osteoarthritis	60	100	96.7	2	Tramadol-ER	Placebo	84
Fishman (2007)	552	Osteoarthritis	61	62	NR	4	Tramadol-ER	Placebo	84
Fleischmann (2001)	129	Osteoarthritis	62	62	364	2	Tramadol-NR	Placebo	91
Friedmann (2011)	412	Osteoarthritis	58	70	NR	2	Oxycodone-ER	Placebo	84
Gana (2006)	1020	Osteoarthritis	58	62	NR	5	Tramadol-ER	Placebo	84
Gilron (2005)	57	Postherpetic neuralgia &painful diabetic neuropathy	50	56	NR	2	Morphine-ER	Placebo	28
Gimbel (2003)	159	Painful diabetic neuropathy			54.5	2	Oxycodone-ER	Placebo	42
Gimbel (2016)	511	Low back pain	59	48	NR	2	Buprenorphine-Buccal	Placebo	84
Gordon (2010)	78	Low back pain	54	47	NR	2	Buprenorphine-PATCH	Placebo	28
Gordon (2010)	79	Mixed neuropathic & non-neuropathic conditions	50	60	170	2	Buprenorphine-PATCH	Placebo	28

Hale (2007)	143	Low back pain	56	55	NR	2	Oxymorphone-ER	Placebo	84
Hale (2010)	268	Low back pain	48	50	NR	2	Hydromorphone-ER	Placebo	84
Hale (2015)	370	Low back pain	51	51	NR	2	Hydrocodone-ER	Placebo	84
Harati (1998)	131	Painful diabetic neuropathy	59	40	NR	2	Tramadol-NR	Placebo	42
Huse (2001)	12	Phantom limb pain	51	17	NR	2	Morphine-ER	Placebo	28
Katz (2007)	205	Low back pain	49	53	NR	2	Oxymorphone-ER	Placebo	84
Katz (2015)	389	Low back pain	49	53	NR	2	Oxycodone-ER	Placebo	84
Khoromi (2007)	55	Lumbar radiculopathy			NR	2	Morphine-ER	Placebo	49
Kawamata (2019)	130	Low back pain	53	45	NR	2	Oxycodone-ER	Placebo	49
Langford (2006)	399	Osteoarthritis	63	67	NR	2	Fentanyl-PATCH	Placebo	42
Lin (2016)	21	Low back pain	41.9	33	97.2	2	Morphine-ER	Placebo	30
Ma (2008)	116	Chronic neck pain	56	38	NR	2	Oxycodone-ER	Placebo	28
Markenson (2005)	107	Osteoarthritis	63	38	NR	2	Oxycodone-ER	Placebo	90
Matsumoto (2005)	491	Osteoarthritis	63	62	NR	4	Oxymorphone-ER Oxycodone-ER	Placebo	28
Mayorga (2016)	98	Osteoarthritis	59	56	NR	4	Oxycodone-ER	Placebo	112
Moran (1991)	15	Osteoarthritis		5	NR	2	Morphine-ER	Placebo	28
Moulin (1996)	61	Chronic post-traumatic pain	40	59	40.8	2	Morphine-ER	Placebo	77
Munera (2010)	315	Osteoarthritis	61	67	NR	2	Buprenorphine-PATCH	Placebo	28
Niesters (2014)	25	Painful diabetic neuropathy	63	41.6	NR	2	Tapentadol-ER	Placebo	28
Norrbrink (2009)	36	Post-traumatic neuralgia	51	78	NR	2	Tramadol-NR	Placebo	28
Peloso (2000)	103	Osteoarthritis	62	40	NR	2	Codeine-ER	Placebo	28
Raja (2002)	76	Postherpetic neuralgia			NR	2	Morphine-ER	Placebo	56
Rauck (2013)	990	Osteoarthritis	50	56	NR	3	Hydromorphone-ER	Placebo	84
Rauck (2014)	302	Low back pain	50	63	NR	2	Hydrocodone-ER	Placebo	84
Rauck (2016)	420	Low back pain	59	64	NR	2	Buprenorphine-Buccal	Placebo	84
Russell (2000)	69	Fibromyalgia	49	94	NR	2	Tramadol-ER	Placebo	42
Schnitzer (2000)	254	Low back pain	47	50	NR	2	Tramadol-NR	Placebo	28
Schwartz (2011)	395	Painful diabetic neuropathy	62	43	76	2	Tapentadol-ER	Placebo	84

1	Serrie (2017)	990	Osteoarthritis	62	69	NR	3	Tapentadol-ER Oxycodone-ER	Placebo	105
2	Simpson (2016)	186	Diabetic neuropathy	63	33	NR	2	Buprenorphine-PATCH	Placebo	84
3	Sindrup (1999)		Painful diabetic neuropathy	57	24	36		Tramadol-ER	Placebo	28
4	Sindrup (2012)	64	Painful polyneuropathy			NR	3	Tramadol-ER	Placebo	28
5	Steiner (2011)	541	Low back pain	49	55	108.6	2	Buprenorphine-PATCH	Placebo	84
6	Thorne (2008)	100	Osteoarthritis	61	55	NR	2	Tramadol-ER	Placebo	28
7	Tominaga (2016)	91	neuropathic & non-neuropathic conditions			NR	2	Tapentadol-ER	Placebo	84
8	Tominaga (2016)	91	Postherpetic neuralgia & painful diabetic neuropathy			NR	2	Tapentadol-ER	Placebo	84
9	Uberall (2012)	240	Low back pain			NR	2	Tramadol-ER	Placebo	28
10	Vinik (2014)	320	Painful diabetic neuropathy	58	41	NR	2	Tapentadol-ER	Placebo	84
11	Vojtassak (2011)	288	Osteoarthritis	66	72	NR	2	Hydromorphone-ER	Placebo	112
12	Vorsanger (2008)	386	Low back pain	47	50	NR	3	Tramadol-ER	Placebo	84
13	Watson (1998)	50	Postherpetic neuralgia	70	44	31	2	Oxycodone-ER	placebo	28
14	Webster (2006)	307	Low back pain	48	61	NR	4	Oxycodone-ER	Placebo	84
15	Wen (2015)	588	Low back pain	48	57	NR	2	Hydrocodone	Placebo	84
16	Wu (2008)	60	postamputation	63	21	51.3	2	Morphine-ER	Placebo	42
17	Opioids versus cannabis for medical use									
18	Frank 2008	192	Neuropathic pain	50	26	76.4	2	THC, Nabilone	Dihydrocodeine	42
19	Cannabis for medical use versus placebo									
20	Andresen (2016)	73	Spinal cord injury-related neuropathic pain	56	26	≥3	2	PEA	Placebo	84
21	Blake (2006)	58	Rheumatoid arthritis pain	63	79	NR	2	THC/CBD, Nabiximols	Placebo	48
22	de Vries (2017)	65	Chronic abdominal pain	53	39	≥3	2	THC, Namisol	Placebo	51
23	Eibach (2020)	68	HIV associated neuropathic pain	50	6	157.2	2	Cannabidiol (CBDV)	Placebo	28
24	Germini (2017)	20	Mixed chronic noncancer pain	83	100	≥6	2	PEA	Placebo	42
25	Hunter (2018)	320	Osteoarthritis	62	51	≥12	2	CBD synthetic gel	Placebo	84
26	Langford (2013)	339	Multiple sclerosis central pain	49	68	65.5	2	THC/CBD, Nabiximols	Placebo	98
27	Markova (2018)	106	Multiple sclerosis with pain (no details)	51.3	80	170.4	2	THC/CBD, Nabiximols	Placebo	84

		(about pain condition)						
NCT00710424 (2006)	297	Diabetic neuropathy	60	38	≥6	2	THC/CBD, Nabiximols	Placebo
Novotna (2011)	241	Multiple sclerosis with pain (no details about pain condition)	49	60	151.2	2	THC/CBD, Nabiximols	Placebo
Nurmikko (2007)	125	Peripheral neuropathic pain	53	59	75.6	2	THC/CBD, Nabiximols	Placebo
Pinsger (2006)	60	Refractory pain related to musculoskeletal system	55	77	240	2	THC, Nabilone	Placebo
Rog (2005)	66	Multiple sclerosis central pain	49	79	138.8	2	THC/CBD	Placebo
Schimrigk (2017)	240	Multiple sclerosis central pain	48	73	NR	2	THC, Marinol	Placebo
Selvarajah (2010)	30	Diabetic neuropathy	56	37	NR	2	THC/CBD, Nabiximols	Placebo
Serpell (2014)	246	Peripheral neuropathy	57	61	75.6	2	THC/CBD, Nabiximols	Placebo
Skrabek (2008)	40	Fibromyalgia	49	NR	NR	2	THC, Nabilone	Placebo
Toth (2012)	26	Diabetic neuropathy	61	46	85.8	2	THC, Nabilone	Placebo
van Amerongen (2018)	24	Multiple sclerosis neuropathic pain and spasticity	54	6	137.4	2	THC, Namisol	Placebo
Wissel (2006)	26	Chronic upper motor neuron syndrome	44.8	69	NR	2	THC, Nabilone	Placebo
Xu (2020)	29	Peripheral neuropathic pain	68	38	≥3	2	CBD	Placebo
Zajicek (2003 and 2005)	657	Multiple sclerosis with pain (no details about pain condition)	51	63	NR	2	THC/CBD, Marinol	Placebo
Zajicek (2012)	279	Multiple sclerosis with pain (no details about pain condition)	52	63	NR	2	THC/CBD	Placebo

eTable 3. Risk of bias assessment of the eligible randomized controlled trials (N = 90 RCTs)

Study	Loss to follow-up (%)	Randomization	Concealment	Blinding of patients	Blinding of care providers	Blinding of data collectors	Blinding of outcome assessors
Afilalo 2010	51	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Andresen 2016	15	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Arai 2015a	49	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Arai 2015b	54	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Babul 2004	50	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Blake 2006	7	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Boureau 2003	15	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Breivik 2010	44	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Burch 2007	24	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Buynak 2010	53	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Caldwell 1999	34	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Caldwell 2002	38	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Christoph 2017	30	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Chu 2012	26	inadequate randomization	inadequate allocation concealment	Yes	No	Yes	Yes
de Vries 2017	25	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
DeLemos 2011	48	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Eibach 2020	18	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Fishman 2007	44	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Fleischmann 2001	71	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Frank 2008	24	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Friedmann 2011	36	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Gana 2006	45	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes

1	Germini 2017	30	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes
2	Gilron 2005	9	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes
3	Gimbel 2003	28	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
4	Gimbel 2016	31	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes
5	Gordon 2010a	35	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes
6	Gordon 2010b	37	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
7	Hale 2007	53	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes
8	Hale 2010	59	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
9	Hale 2015	20	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
10	Harati 1998	37	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
11	Hunter 2018	26	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes
12	Huse 2001	17	inadequate randomization	inadequate allocation concealment	No	No	No
13	Katz 2007	42	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes
14	Katz 2015	43	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
15	Kawamata 2019	37	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes
16	Khoromi 2007	33	adequate randomization	inadequate allocation concealment	Yes	Yes	Yes
17	Langford 2006	52	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
18	Langford 2013	12	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes
19	Lin 2016	0	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes
20	Ma 2008	90	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes
21	Markenson 2005	66	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
22	Markova 2018	9	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes
23	Matsumoto 2005	45	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
24	Mayorga 2016	61	adequate randomization	adequate allocation concealment	Yes	Yes	Yes
25	Moran 1991	25	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes

Moulin 1996	25	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Munera 2010	51	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
NCT00710424 2006	23	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Niesters 2014	0	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Norrbrink 2009	36	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Novotna 2011	7	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Nurmikko 2007	16	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Peloso 2000	36	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Pinsger 2006	30	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Raja 2002	42	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Rauck 2013	51	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	No
Rauck 2014	39	inadequate randomization	adequate allocation concealment	Yes	Yes	No	No
Rauck 2016	9	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Rog 2005	3	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Russell 2000	1	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Schimrigk 2017	26	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Schnitzer 2000	43	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Schwartz 2011	33	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Selvarajah 2010	20	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Serpell 2014	30	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Serrie 2017	46	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Simpson 2016	33	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Sindrup 1999	20	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Sindrup 2012	8	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Skrabek 2008	18	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes

Steiner 2011	32	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Thorne 2008	25	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Tominaga 2016a	13	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Tominaga 2016b	9	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Toth 2012	4	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Uberall 2012	25	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
van Amerongen 2018	4	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Vinik 2014	29	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Vojtassak 2011	31	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Vorsanger 2008	38	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Watson 1998	22	inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Webster 2006	54	adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Wen 2015	25	inadequate randomization	inadequate allocation concealment	Yes	Yes	Yes	Yes
Wissel 2006	15	Inadequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Wu 2008	41	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Xu 2020	21	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Zajicek 2003 & 2005	4	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes
Zajicek 2012	20	Adequate randomization	adequate allocation concealment	Yes	Yes	Yes	Yes

eTable 4. Network estimates and their certainty in evidence (GRADE) evaluating the effects of opioid and cannabis for medical use therapy in patients with chronic non-cancer pain across different outcomes

Outcome	Comparison	Direct Estimate MD (95% CI)	Indirect Estimate MD (95% CI)	Network Estimate* MD (95% CrI))	GRADE
Pain (VAS 0-10)	Opioid vs placebo	<u>-0.84 (-0.99, -0.69)</u>	<u>-0.83 (-0.97, -0.70)</u>	<u>-0.83 (-0.97, -0.70)</u>	Moderate ²
	Cannabis for medical use vs placebo	<u>-0.63 (-0.94, -0.32)</u>	<u>-0.59 (-0.88, -0.32)</u>	<u>-0.60 (-0.87, -0.33)</u>	Low ^{2,8}
	Cannabis for medical use vs opioid	0.13 (-0.54, 0.80)	0.24 (-0.07, 0.55)	0.23 (-0.06, 0.53)	Low ^{1,8}
Physical function (SF 0-100)	Opioid vs placebo	<u>2.38 (1.05, 3.72)</u>	—	<u>2.05 (1.01, 3.29)</u>	Moderate ⁸
	Cannabis for medical use vs placebo	<u>3.00 (0.08, 5.91)</u>	—	<u>2.52 (0.37, 4.91)</u>	Moderate ⁸
	Cannabis for medical use vs opioid	—	0.47 (-1.97, 2.99)	0.47 (-1.97, 2.99)	Moderate ²
Emotional function (SF 0-100)	Opioid vs placebo	-0.00 (-1.09, 1.09)	—	-0.15 (-1.10, 0.92)	High
	Cannabis for medical use vs placebo	0.72 (-1.01, 2.45)	—	0.70 (-1.42, 2.84)	Moderate ⁸
	Cannabis for medical use vs opioid	—	0.85 (-1.55, 3.18)	0.85 (-1.55, 3.18)	Low ^{2,8}
Role function (SF 0-100)	Opioid vs placebo	0.91 (-1.17, 2.98)	—	0.94 (-1.26, 3.17)	Moderate ⁸
	Cannabis for medical use vs placebo	1.27 (-12.39, 14.93)	—	0.88 (-3.78, 6.05)	Moderate ⁸
	Cannabis for medical use vs opioid	—	-0.05 (-5.16, 5.60)	-0.05 (-5.16, 5.60)	Moderate ⁸
Social function (SF 0-100)	Opioid vs placebo	0.47 (-1.47, 2.41)	—	1.17 (-1.72, 4.58)	Moderate ⁸
	Cannabis for medical use vs placebo	-1.82 (-5.79, 2.15)	—	1.70 (-3.28, 8.13)	Moderate ⁸
	Cannabis for medical use vs opioid	—	0.55 (-5.34, 7.41)	0.55 (-5.34, 7.41)	Moderate ⁸
Sleep quality (0-100)	Opioid vs placebo	<u>5.55 (2.67, 8.43)</u>	—	<u>5.46 (2.62, 8.59)</u>	Moderate ²
	Cannabis for medical use vs placebo	<u>6.04 (1.43, 10.66)</u>	—	<u>5.95 (1.82, 10.24)</u>	Low ^{2,8}
	Cannabis for medical use vs opioid	—	0.49 (-4.72, 5.59)	0.49 (-4.72, 5.59)	Low ^{2,8}
Outcome	Comparison	Direct Estimate OR (95% CI)	Indirect Estimate OR (95% CI)	Network Estimate* OR (95% CrI)	GRADE
Discontinuations due to adverse events (enriched)	Opioid vs placebo	<u>1.39 (1.04, 1.86)</u>	-	1.25 (0.91, 1.67)	Low ^{1,8}
	Cannabis for medical use vs placebo	5.00 (0.25, 101.7)	-	0.96 (0.09, 10.80)	Low ^{1,8}
	Cannabis for medical use vs opioid		0.77 (0.07, 8.83)	0.77 (0.07, 8.83)	Low ^{1,8}
Discontinuations due to adverse events (non-enriched)	Opioid vs placebo	<u>3.58 (3.00, 4.27)</u>	<u>3.27 (2.70, 3.93)</u>	<u>3.27 (2.71, 3.90)</u>	Moderate ¹
	Cannabis for medical use vs placebo	<u>2.47 (1.49, 4.11)</u>	<u>1.78 (1.15, 2.63)</u>	<u>1.80 (1.19, 2.63)</u>	High
	Cannabis for medical use vs opioid	0.50 (0.16, 1.61)	<u>0.54 (0.34, 0.84)</u>	<u>0.55 (0.36, 0.83)</u>	Moderate ¹

* Imprecision only incorporated at network level not at direct or indirect.

Abbreviations: MD: Mean difference; 95 CI%: 95% Confidence Intervals; GRADE Certainty of Evidence.

GRADE Assessment: Reasons for downgrading direct evidence:

1. Rated down due to risk of bias
2. Rated down due to inconsistency
3. Rated down due to imprecision (effects were rated down if the associated measure of precision included no effect [a mean difference of 0])
4. Rated down due to indirectness
5. Rated down due to publication bias

Reasons for downgrading indirect evidence:

6. Rated down for intransitivity

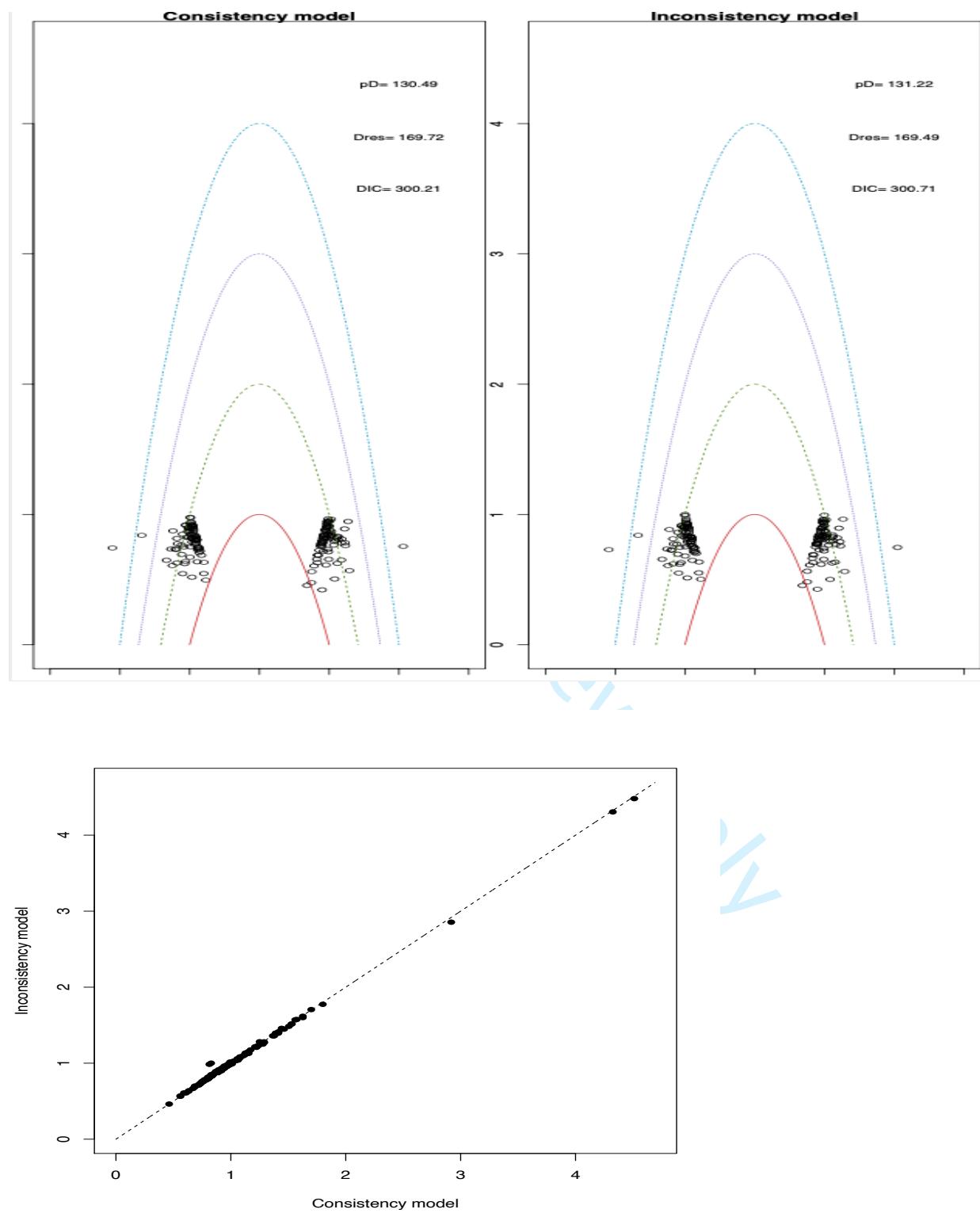
Reasons for downgrading network evidence

7. Rated down due to incoherence

8. Rated down due to imprecision (either due to inclusion of the null value in the 95%CI, or because the evidence is provided by a small number of patients – a total number of patients less than the optimal information size [n=300])

When two of the same superscripts are listed with an estimate of treatment effect (e.g. ^{1,1}), this means the certainty of evidence (GRADE) was downgraded for 2 levels (-2), instead of one (-1)

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eFigure 1. Pain, random effects consistency and inconsistency model

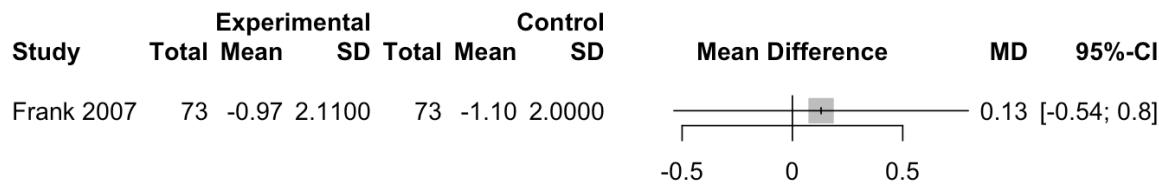


eTable 5. Pain, node splitting outputs

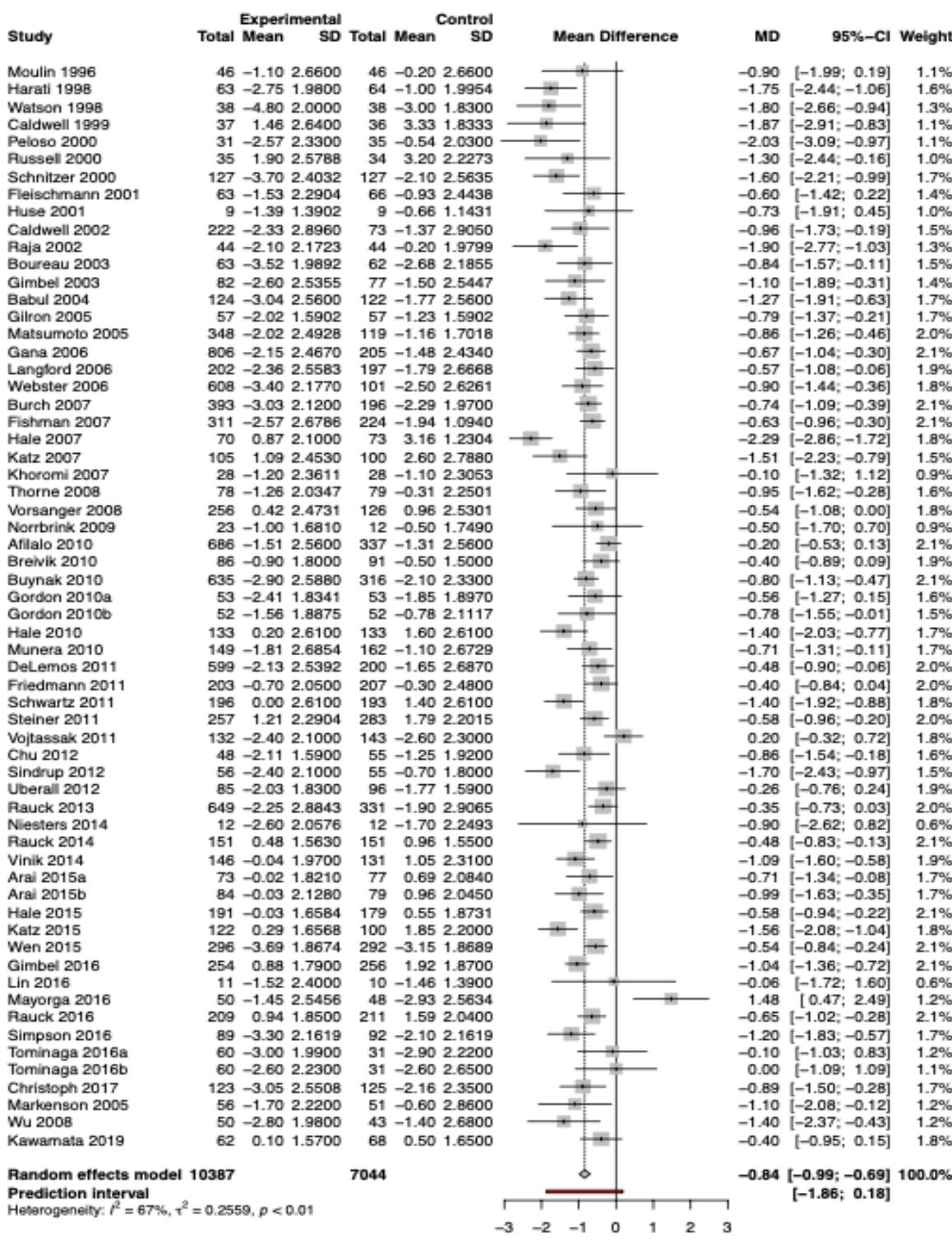
Comparison of direct versus indirect evidence - Mean change in pain VAS from baseline

Comparisons	Direct evidence	Indirect evidence
Cannabis for medical use vs. Opioids	0.13 (-0.54, 0.80)	0.23 (-0.10, 0.55)

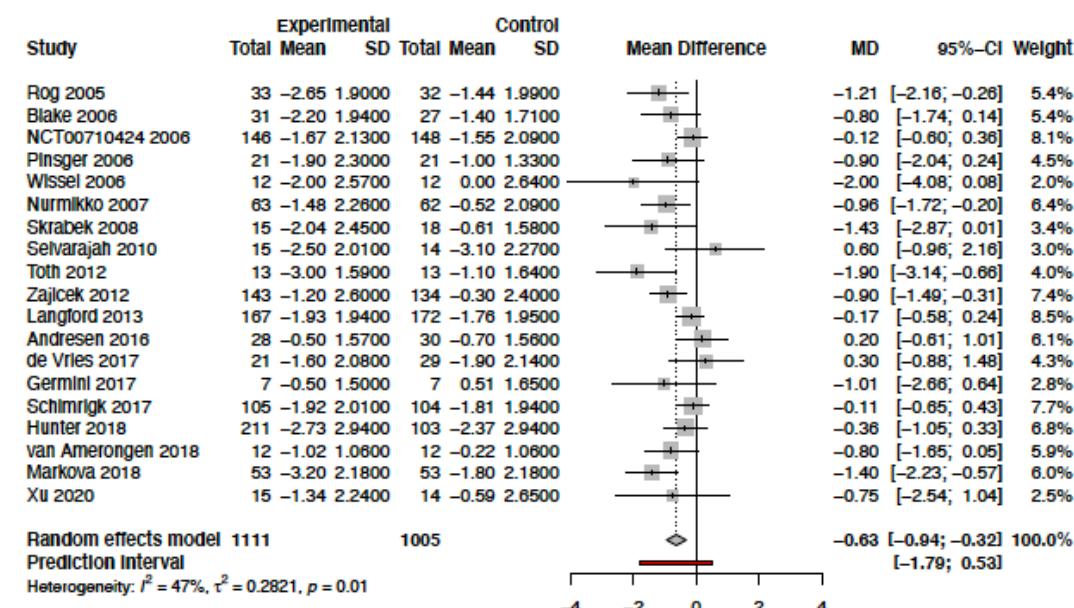
P-value = 0.792

Direct evidence forest plot

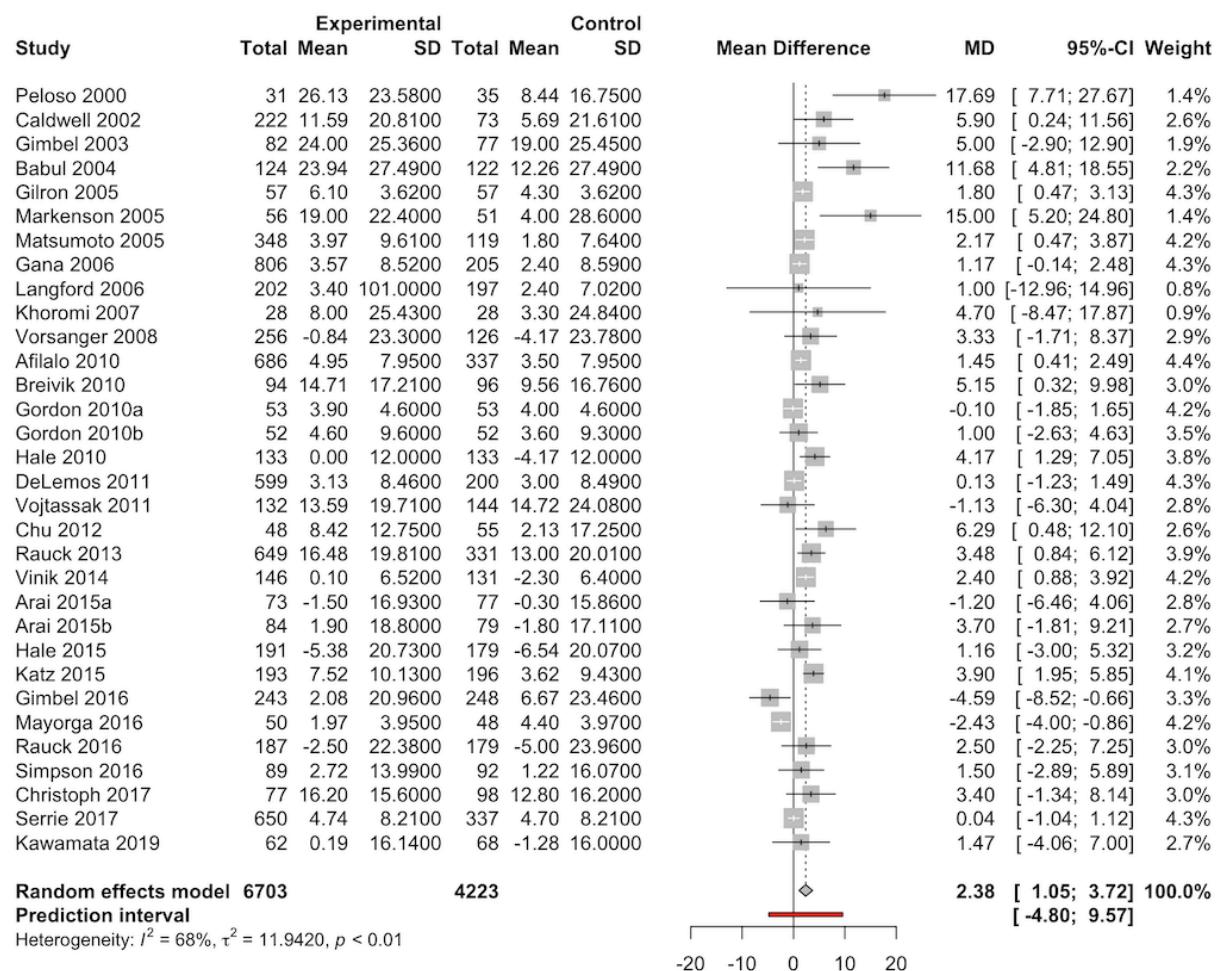
eFigure 2. Pain, opioids versus placebo pairwise meta-analysis random effect model



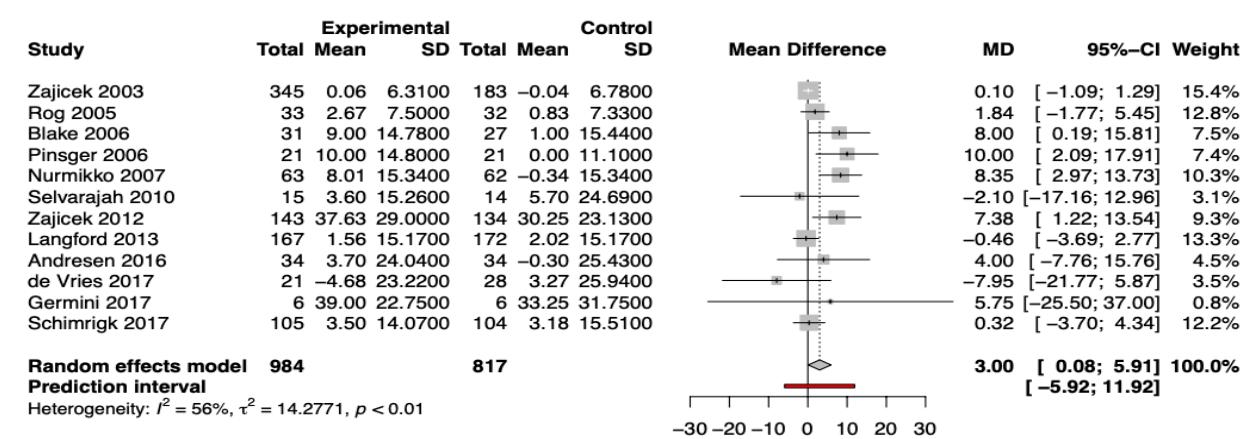
1
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5 eFigure 3. Pain, cannabis for medical use versus placebo pairwise meta-analysis random effects model
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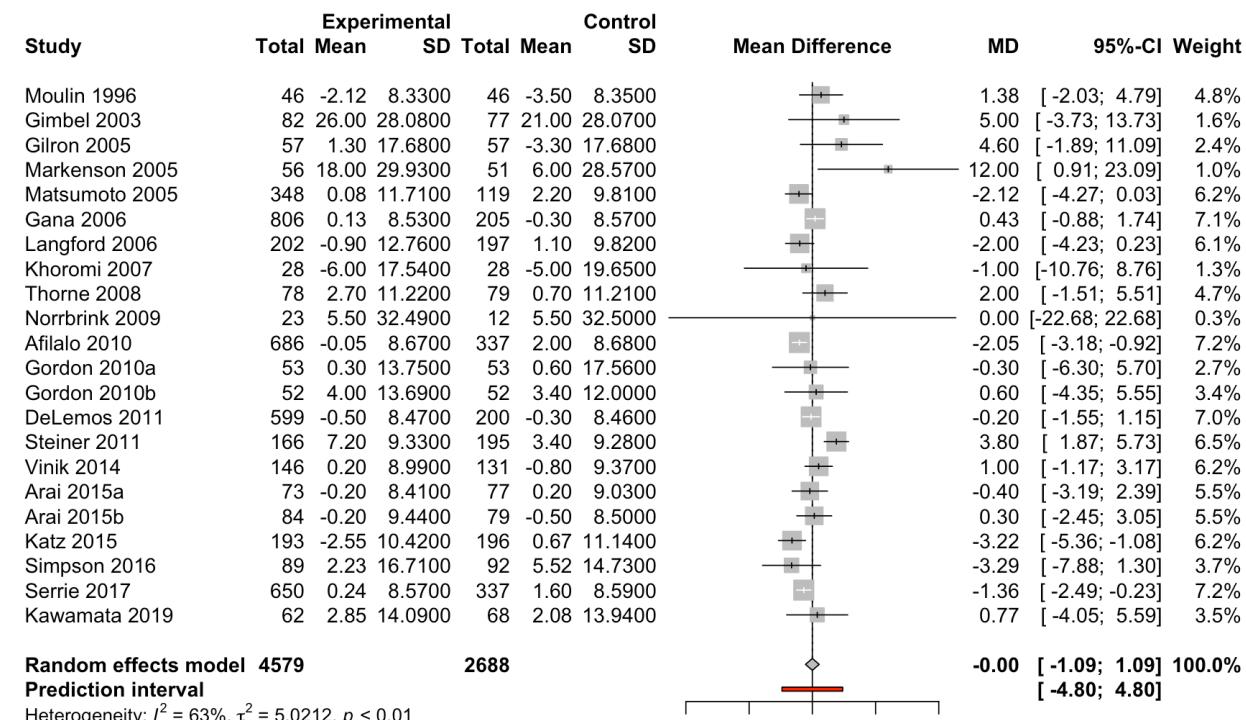
eFigure 4. Physical functioning, opioids versus placebo pairwise meta-analysis random effect model



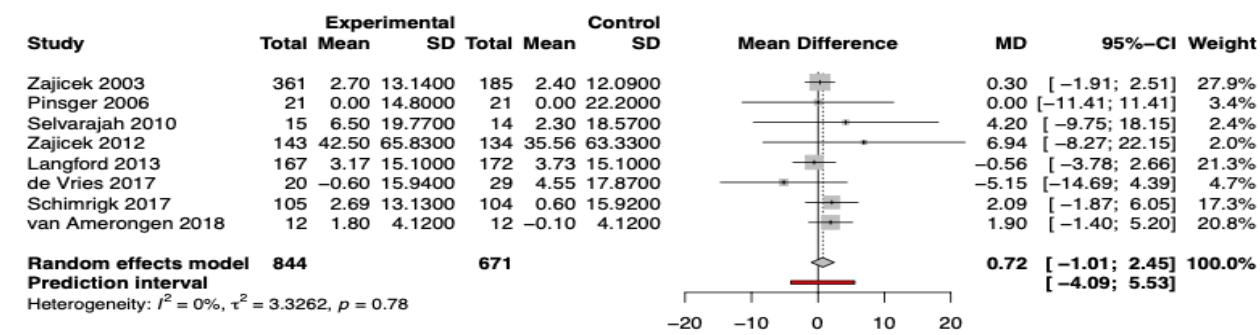
eFigure 5. Physical functioning, cannabis for medical use versus placebo pairwise meta-analysis random effect model



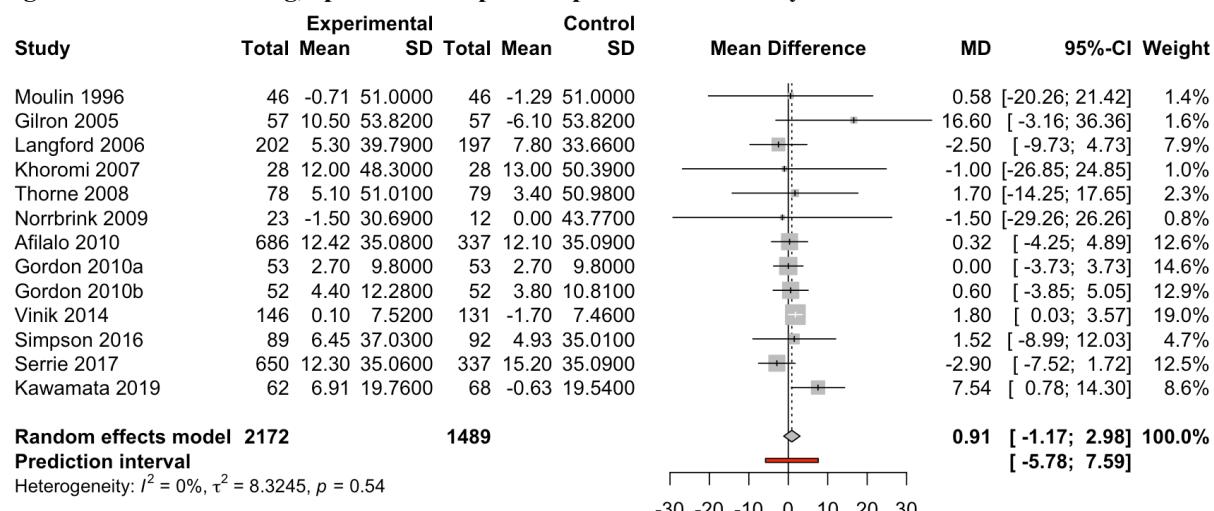
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5 eFigure 6. Emotional functioning, opioids versus placebo pairwise meta-analysis random effect model
6



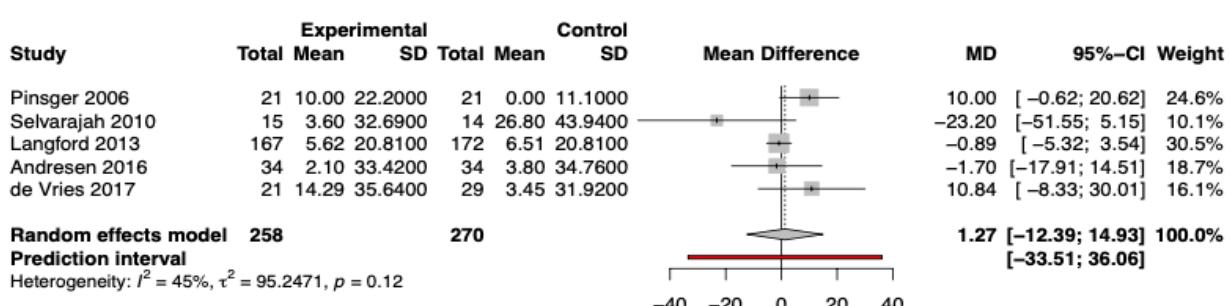
31 eFigure 7. Emotional functioning, cannabis for medical use versus placebo pairwise meta-analysis random
32 effect model
33



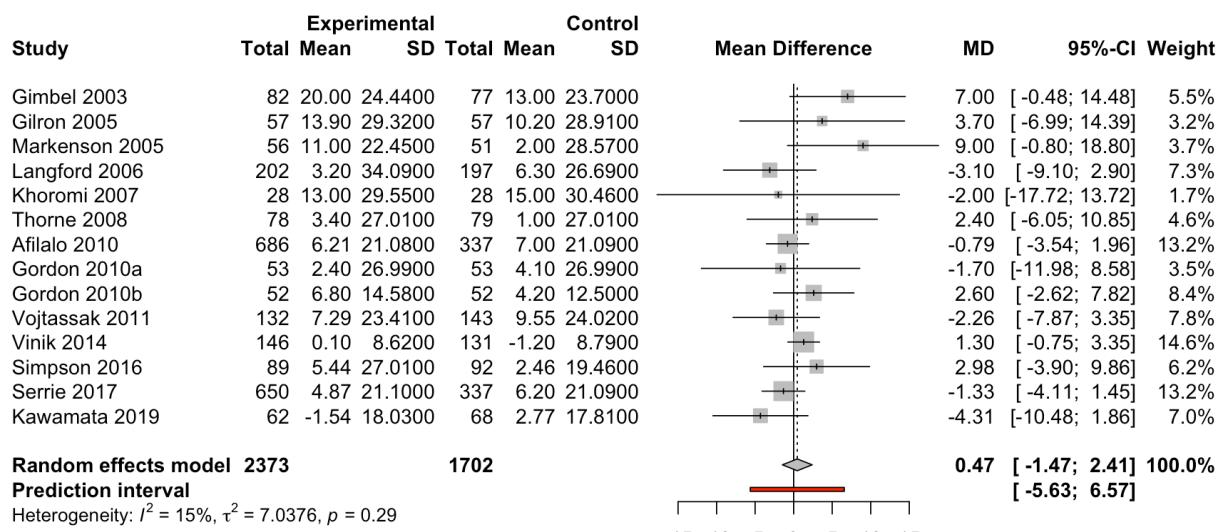
eFigure 8. Role functioning, opioids versus placebo pairwise meta-analysis random effect model



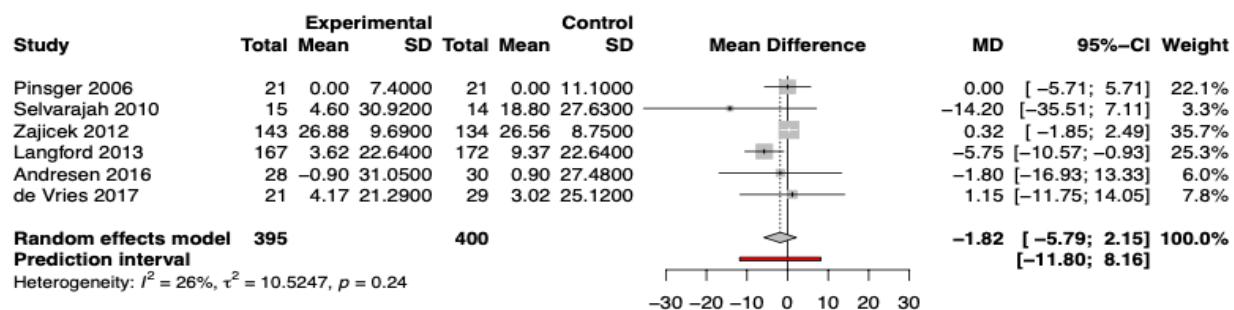
eFigure 9. Role functioning, cannabis for medical use versus placebo pairwise meta-analysis random effect model



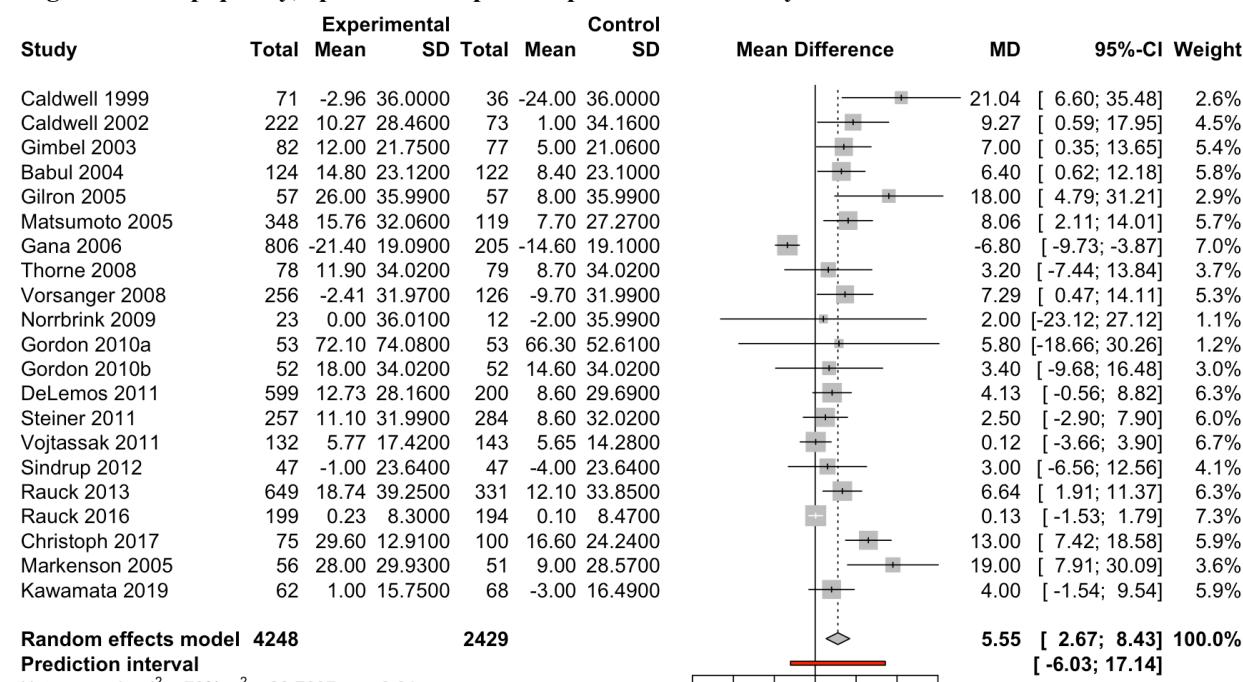
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5 eFigure 10. Social functioning, opioids versus placebo pairwise meta-analysis random effect model
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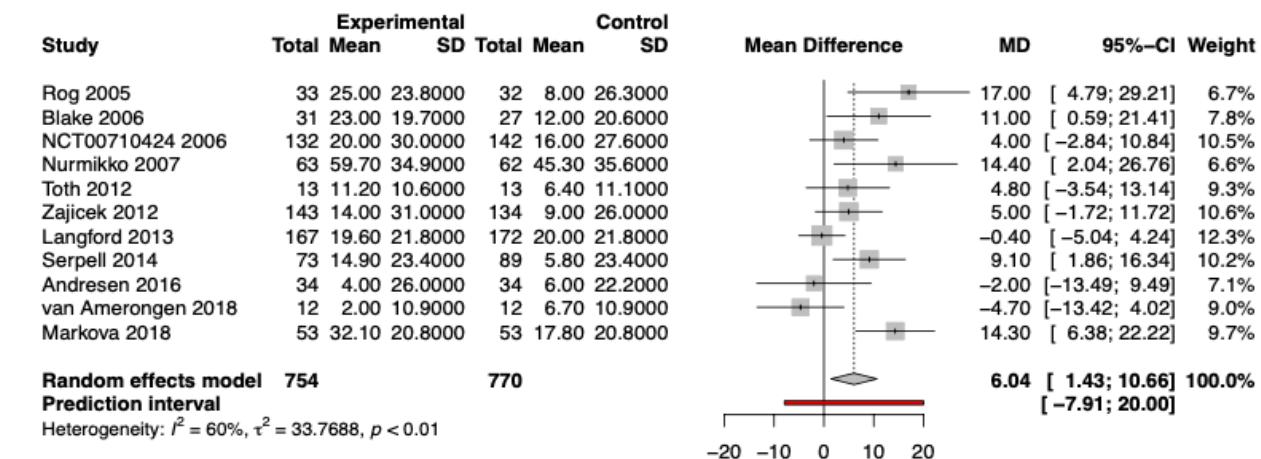
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25 eFigure 11. Social functioning, cannabis for medical use versus placebo pairwise meta-analysis random effect
26 model
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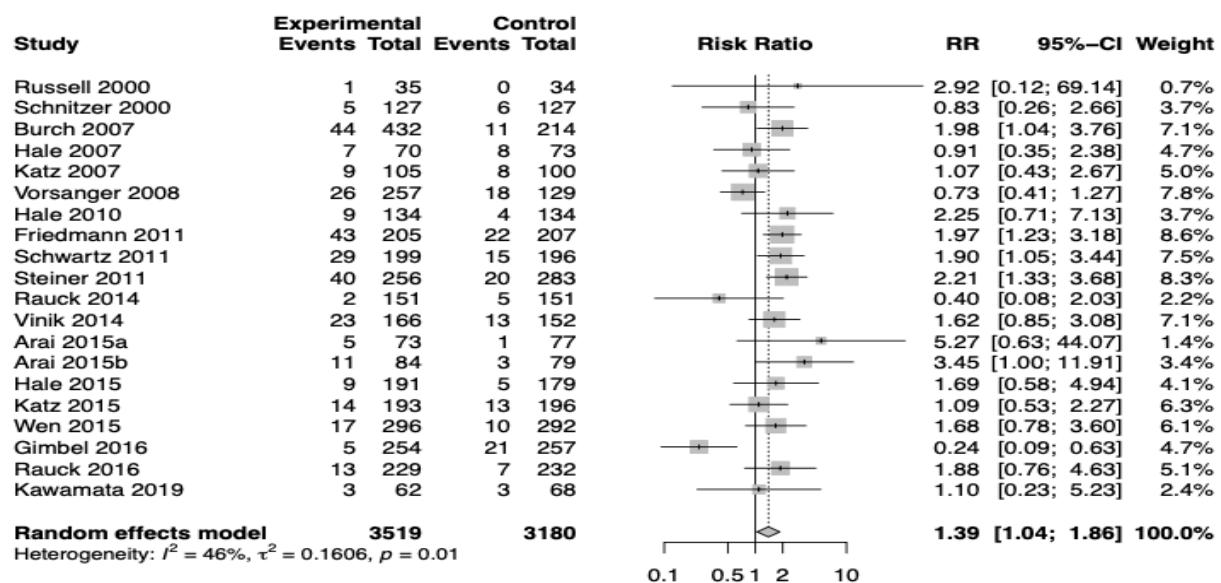
eFigure 12. Sleep quality, opioids versus placebo pairwise meta-analysis random effect model



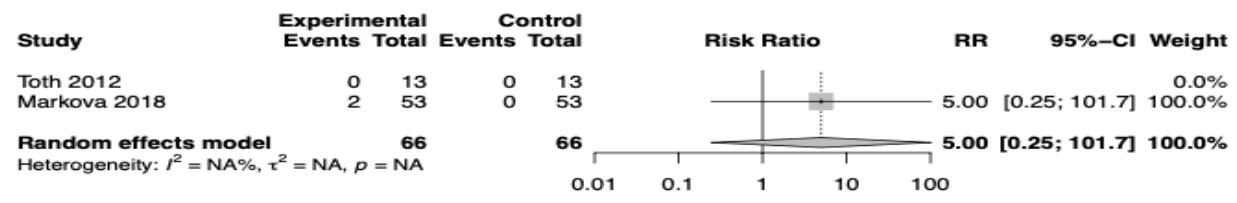
eFigure 13. Sleep quality, cannabis for medical use versus placebo pairwise meta-analysis random effect model



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5 eFigure 14. Discontinuations due to adverse events (enriched trials), opioids versus placebo pairwise meta-analysis random effect model
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28 eFigure 15. Discontinuations due to adverse events (enriched trials), cannabis for medical use versus placebo
29 pairwise meta-analysis random effect model
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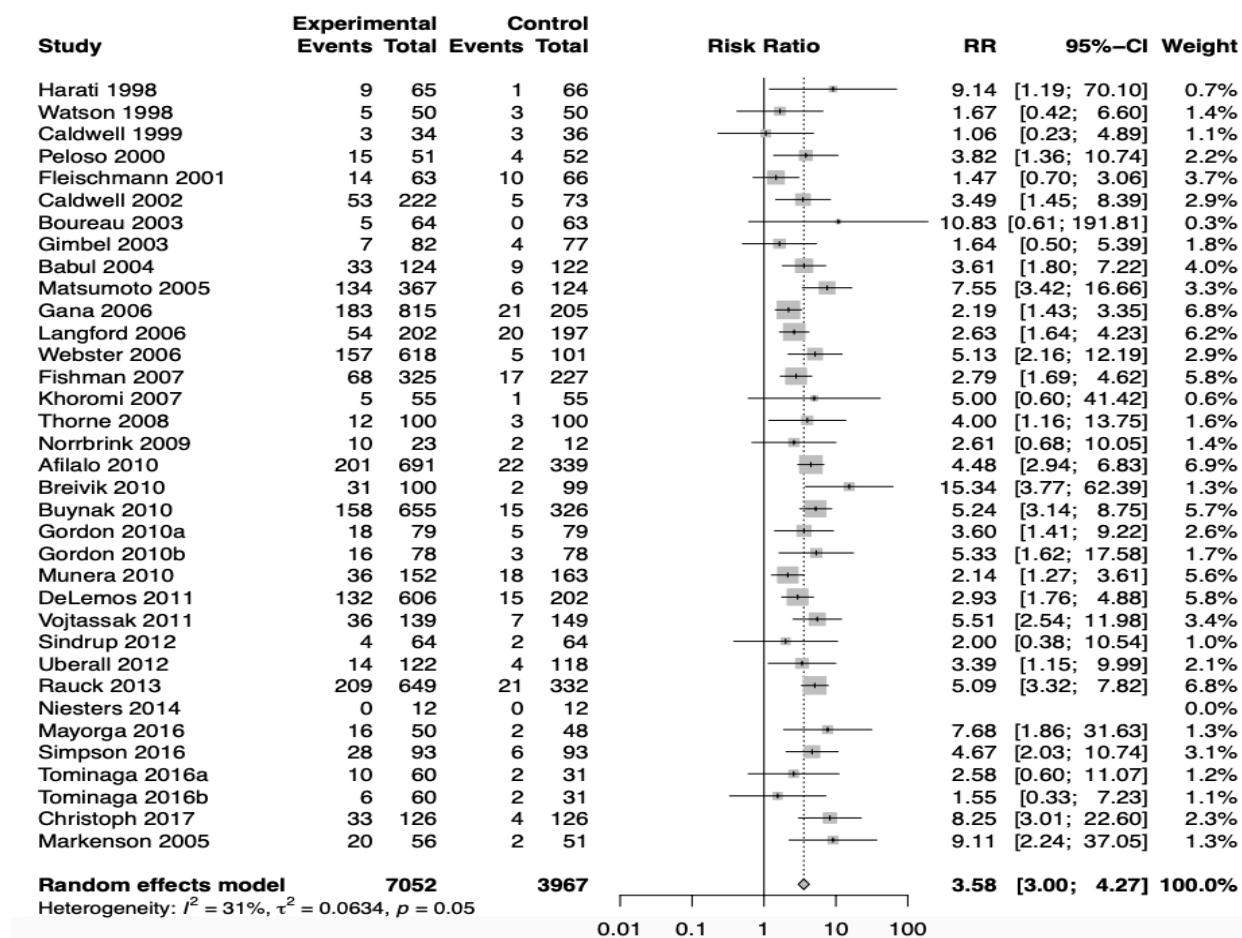
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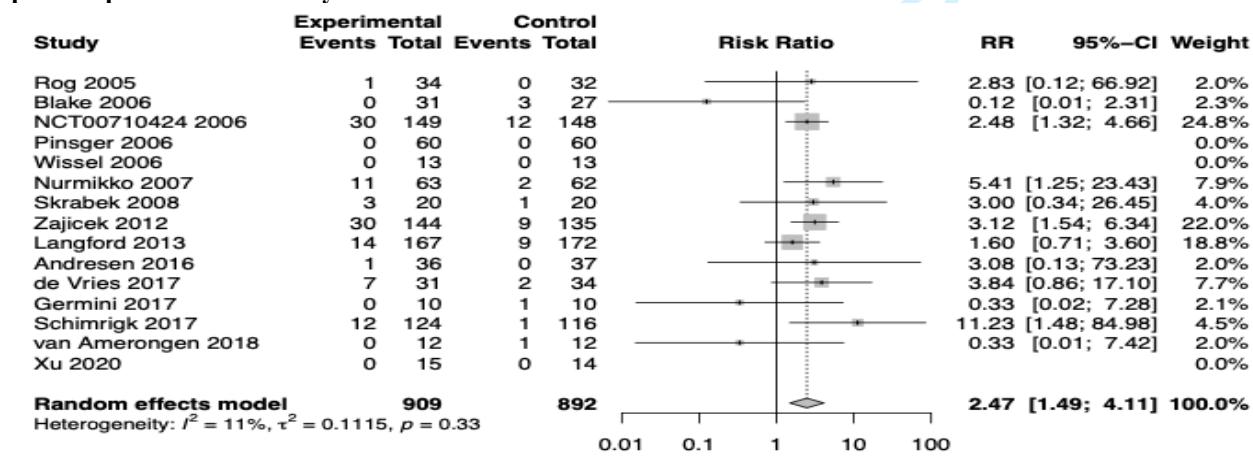
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eFigure 16. Discontinuations due to adverse events (non-enriched trials), opioids versus placebo pairwise meta-analysis random effect model



eFigure 17. Discontinuations due to adverse events (non-enriched trials), cannabis for medical use versus placebo pairwise meta-analysis random effect model



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5 **eAppendix 4: Reference list of cannabis for medical use studies with incomplete EQ-5D and SF-36 general**
6 **health data**

7 **EQ-5D:**

- 8 1. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel- group study
9 of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central
10 neuropathic pain in patients with multiple sclerosis. *J Neurol* 2013;260(4):984-97. doi: 10.1007/s00415-012-
11 6739-4 [published Online First: 2012/11/28]
12 2. Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel- group,
13 enriched-design study of nabiximols* (Sativex((R))), as add-on therapy, in subjects with refractory spasticity
14 caused by multiple sclerosis. *Eur J Neurol* 2011;18(9):1122-31. doi: 10.1111/j.1468-1331.2010.03328.x
15 [published Online First: 2011/03/03]
16 3. NCT00710424. A Study of Sativex® for Pain Relief Due to Diabetic Neuropathy:
17 <https://ClinicalTrials.gov/show/NCT00710424>, 2006.
18 4. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of
19 cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding
20 factor. *Diabetes Care* 2010;33(1):128-30. doi: 10.2337/dc09-1029 [published Online First: 2009/10/08]
21 5. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind,
22 placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic
23 peripheral neuropathic pain. *Pain* 2012;153(10):2073-82. doi: 10.1016/j.pain.2012.06.024 [published Online
24 First: 2012/08/28]

25 **SF-36 General health:**

- 26 1. Frank B, Serpell MG, Hughes J, et al. Comparison of analgesic effects and patient tolerability of nabilone and
27 dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ*
28 2008;336(7637):199-201. doi: 10.1136/bmj.39429.619653.80 [published Online First: 2008/01/10]
29 2. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel- group study
30 of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central
31 neuropathic pain in patients with multiple sclerosis. *J Neurol* 2013;260(4):984-97. doi: 10.1007/s00415-012-
32 6739-4 [published Online First: 2012/11/28]
33 3. Markova J, Essner U, Akmaz B, et al. Sativex((R)) as add-on therapy vs. further optimized first-line
34 ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled
35 randomised clinical trial. *Int J Neurosci* 2019;129(2):119-28. doi: 10.1080/00207454.2018.1481066 [published
36 Online First: 2018/05/25]
37 4. Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel- group,
38 enriched-design study of nabiximols* (Sativex((R))), as add-on therapy, in subjects with refractory spasticity
39 caused by multiple sclerosis. *Eur J Neurol* 2011;18(9):1122-31. doi: 10.1111/j.1468-1331.2010.03328.x
40 [published Online First: 2011/03/03]
41 5. NCT00710424. A Study of Sativex® for Pain Relief Due to Diabetic Neuropathy:
42 <https://ClinicalTrials.gov/show/NCT00710424>, 2006.
43 6. Schimrigk S, Marziniak M, Neubauer C, et al. Dronabinol Is a Safe Long-Term Treatment Option for
44 Neuropathic Pain Patients. *European neurology* 2017;78(5-6):320-29. doi: 10.1159/000481089 [published
45 Online First: 2017/10/27]
46 7. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of
47 cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding
48 factor. *Diabetes Care* 2010;33(1):128-30. doi: 10.2337/dc09-1029 [published Online First: 2009/10/08]

eTable 6. ICEMAN criteria for assessing the credibility of subgroup effects

Criteria	Subgroup effects of neuropathic vs non-neuropathic pain for outcomes below		
	Pain	Social function	Discontinuation due to adverse events (non-enriched)
1: Is the analysis of effect modification based on comparison within rather than between trials?	Between-study	Between-study	Between-study
2: For within-trial comparisons, is the effect modification similar from trial to trial?	Not applicable	Not applicable	Not applicable
3: For between-trial comparisons, is the number of trials large?	Large (55 studies with non-neuropathic pain; 26 studies with neuropathic pain)	Large (11 studies with non-neuropathic pain; 8 study with neuropathic pain)	Large (33 studies with non-neuropathic pain; 17 studies with neuropathic pain)
4: Was the direction of effect modification correctly hypothesized a priori?	Probably no (opposite)	Probably no (opposite)	Probably no (opposite)
5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification?	Chance an unlikely explanation ($p=0.004$)	Chance a likely explanation ($p=0.047$)	Chance a very likely explanation ($p=0.052$)
6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?	Probably no (5 factors)	Probably no (5 factors)	Probably no (5 factors)
7: Did the authors use a random effects model?	Definitely yes	Definitely yes	Definitely yes
8: If the effect modifier is a continuous variable, were arbitrary cut points avoided?	NA	NA	NA
9 Optional: Are there any additional considerations that may increase or decrease credibility?			
The effect modification persisted after adjustment for other potential effect modifiers	NA	NA	NA
The effect modification is consistent across related outcomes	Yes	Yes	Yes
A sensitivity analysis suggested robustness to relevant assumptions	NA	NA	NA
Effect modification supported by external evidence	NA	NA	NA
“Dose-response effect” across levels of the effect modifier	NA	NA	NA
Risk of bias of the main effects of the individual RCTs or the meta-analysis	NA	NA	NA
The meta-analysis had had exceptionally high power to detect the effect modification	NA	NA	NA
Overall credibility	Low	Very low	Very low

eTable 7. Subgroup analysis for pain and secondary outcomes with moderate to high certainty evidence

Subgroup factors		Pain relief			Physical functioning			Role functioning			Social functioning			Discontinuations due to adverse events (non-enriched)			
		No studies	WMD 95% CrI	p-value	No studies	WMD 95% CrI	p-value	No studies	WMD 95% CrI	p-value	No studies	WMD 95% CrI	p-value	No studies	OR 95% CrI	p-value	
Clinical condition	Neuropathic	26	0.74 (0.30,1.12)	0.004	11	-0.67 (-4.46, 3.28)	0.55	8	-4.66 (-21.16,5.49)	0.10	8	-8.09 (-16.89,-0.69)	0.047	17	0.91 (0.48, 1.76)	0.052	
	Non-neuropathic	55	-0.12 (-0.55,0.30)		32	0.97 (-2.67, 4.72)		9	9.81 (-1.55,21.10)		11	1.01 (-3.01,4.75)		33	*0.34* (0.15, 0.67)		
Length of follow-u	≤ 2 months	39	0.04 (-0.36,0.45)	0.228	17	2.35 (-2.72,6.56)	0.59	10	8.59 (-3.64,20.37)	0.14	10	-0.31 (-8.27,7.79)	0.70	29	*0.42* (0.20, 0.79)	0.338	
	>2 months	43	0.41 (-0.04,0.85)		27	-0.75 (-3.83, 2.38)		8	-2.48 (-11.89, 5.23)		10	-2.26 (-9.50,2.29)		22	0.65 (0.37, 1.16)		
Adequate randomization	Yes	49	0.14 (-0.25,0.53)	0.506	31	0.36 (-2.14, 3.03)	0.95	11	2.92 (-9.96,15.78)	0.55	15	0.07 (-4.45,4.34)	0.35	36	*0.48* (0.27, 0.79)	0.375	
	No	33	0.37 (-0.19,0.92)		13	0.01 (-10.42, 9.03)		7	-4.55 (-26.29,14.71)		5	-6.93 (-21.75,6.27)		15	0.77 (0.31, 1.86)		
Adequate concealment	Yes	59	0.25 (-0.08,0.58)	NA	34	0.87 (-1.43, 3.37)	NA	13	-0.81 (-6.88,5.75)	NA	16	-2.02 (-6.75,1.60)	NA	39	*0.51* (0.31, 0.79)	NA	
	No	NA	NA		NA	NA		NA	NA		NA	NA		NA	NA		
Industry funded trials	Yes	65	0.23 (-0.13,0.58)	0.877	35	0.72 (-2.02, 3.52)	0.36	13	-0.71 (-6.86,5.72)	0.66	16	-0.62 (-4.94,2.69)	1.00	39	*0.55* (0.33, 0.92)	0.484	
	No	10	0.32 (-0.78,1.39)		6	-4.57 (-15.20, 6.66)		5	-4.59 (-18.01,14.04)		4	-0.62 (-10.78,10.11)		6	0.77 (0.09, 3.75)		
Loss to follow-up	High ($\geq 20\%$)	60	*0.53* (0.08,0.98)	0.074	34	-0.39 (-5.45, 4.52)	0.51	14	1.40 (-3.77, 8.21)	0.21	15	-3.31 (-8.10,1.48)	0.66	37	0.63 (0.36, 1.11)	0.790	
	Low (<20%)	22	-0.09 (-0.64,0.38)		10	0.86 (-3.74, 6.97)		4	-18.49 (-51.56,8.85)		5	0.32 (-17.97,13.13)		14	0.79 (0.13, 2.97)		
Study design	Enrichment	22	-0.65 (-1.65,0.35)	0.093	NA	NA	NA	3	-22.92 (-61.99,16.11)	0.24	3	-14.19 (-40.56,12.39)	0.36	NA			
	Non-enrichment	60	0.25 (-0.07,0.57)		34	0.37 (-2.57, 3.19)		15	0.55 (-5.34, 7.41)		17	-1.54 (-6.21,2.32)		NA			

All values in bold are statistically significant at the 0.05 significance level. * = unless otherwise indicated. Results are cannabis for medical use versus opioids. p-value based on test of interaction

eTable 8. Subgroup analysis for secondary outcomes with low certainty evidence

Subgroup factors		Emotional functioning				Sleep quality				Discontinuations due to AEs (enriched studies)			
		No studies	WMD	95% CrI	p-value	No studies	WMD	95% CrI	p-value	No studies	OR	95% CrI	p-value
Clinical condition	Neuropathic	10	0.15	(−4.07, 4.56)	0.783	10	−3.44	(−12.56, 6.03)	0.323	4	NA	NA	NA
	Non-neuropathic	19	0.91	(−2.47, 4.08)		21	2.68	(−5.25, 10.38)		18	NA	NA	
Length of follow-up	≤ 2 months	13	0.80	(−4.77, 5.19)	0.965	16	−0.28	(−7.45, 7.26)	0.848	4			
	>2 months	17	0.93	(−2.11, 4.08)		16	0.75	(−6.96, 8.09)		18			
Adequate randomization	Yes	18	2.55	(−0.74, 5.64)	0.119	21	0.04	(−6.62, 6.70)	0.638	11	NA	NA	NA
	No	12	−1.14	(−4.54, 2.20)		11	3.21	(−8.92, 13.92)		11	2.05	(0.09, 93.28)	
Adequate concealment	Yes	22	1.44	(−0.91, 3.62)	NA	25	0.20	(−6.32, 6.44)	NA	15	0.91	(0.08, 10.88)	NA
	No	NA	NA	NA		NA	NA	NA		NA	NA	NA	
Industry funded trials	Yes	24	2.27	(−1.19, 5.68)	0.363	29	0.71	(−4.94, 6.20)	0.684	21	0.79	(0.07, 8.97)	NA
	No	5	−1.71	(−9.86, 5.86)		3	−3.12	(−20.25, 14.88)		NA	NA	NA	
Loss to follow-up	High (≥20%)	25	0.38	(−2.41, 3.04)	0.997	20	0.86	(−9.30, 10.66)	0.958	NA	NA	NA	NA
	Low (<20%)	5	0.36	(−8.02, 9.38)		12	1.13	(−11.54, 12.53)		5	0.65	(0.04, 10.18)	
Study design	Enrichment	7	4.05	(−10.97, 19.04)	0.695	6	7.27	(−4.35, 17.38)	0.184	−	−	−	−
	Non-enrichment	23	1.02	(−1.32, 3.12)		26	−1.21	(−7.49, 4.96)		−	−	−	

Results are cannabis for medical use versus opioids. Inadequate concealment not applicable because all cannabis for medical use trials had adequate concealment.

p-value based on test of interaction

eTable 9. Network meta-regression for pain outcome, length of follow-up and sample size

Pain relief, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Cannabis for medical use
Unadjusted model			
Placebo	Adjusted model		-0.60 (-0.87, -0.33)
		-1.39 ¹ (-2.04, -0.76)	
		-1.21 ² (-1.53, -0.91)	0.18 ³ (-0.55, 0.89)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		-0.60 (-0.87, -0.33)
		-0.91 ¹ (-1.37, -0.46)	
		-0.97 ² (-1.15, -0.78)	-0.06 ³ (-0.54, 0.44)

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

eTable 10. Network meta-regression for secondary outcomes, length of follow-up and sample size

Physical functioning, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Cannabis for medical use
Unadjusted model			
Placebo	Adjusted model		2.52 (0.37, 4.91)
		7.23 ¹ (2.10, 12.77)	
		3.00 ² (0.43, 5.84)	-4.20 ³ (-10.32, 1.54)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		2.52 (0.37, 4.91)
		4.19 ¹ (0.94, 7.57)	
		2.75 ² (1.16, 4.65)	-1.44 (-5.08, 2.33)

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

Emotional functioning, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Cannabis for medical use
		Unadjusted model	
Placebo	Adjusted model		0.70 (-1.42, 2.84)
Cannabis for medical use		0.96 ¹ (-4.81, 6.57)	
Opioids		0.32 ² (-2.68, 3.59)	-0.67 ³ (-6.78, 5.92)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		0.70 (-1.42, 2.84)
Cannabis for medical use		1.11 ¹ (-2.04, 4.24)	
Opioids		0.59 ² (-0.99, 2.31)	-0.50 ³ (-3.98, 3.06)

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

Role functioning, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Cannabis for medical use
		Unadjusted model	
Placebo	Adjusted model		0.88 (-3.78, 6.05)
Cannabis for medical use		14.41 ¹ (-0.89, 31.01)	
Opioids		2.22 ² (-2.95, 8.49)	-12.11 ³ (-29.35, 4.07)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		0.88 (-3.78, 6.05)
Cannabis for medical use		5.40 ¹ (-5.80, 16.94)	
Opioids		2.25 ² (-0.87, 5.72)	-3.13 ³ (-14.98, 8.65)

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

Social functioning, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Cannabis for medical use
		Unadjusted model	
Placebo	Adjusted model		1.70 (-3.28, 8.13)
Cannabis for medical use		2.43 ¹ (-7.21, 12.74)	
Opioids		1.98 ² (-3.14, 6.89)	-0.37 ³ (-11.76, 10.10)
Covariate, sample size		Unadjusted model	
Placebo	Adjusted model		1.70 (-3.28, 8.13)
Cannabis for medical use		0.16 ¹ (-7.66, 8.04)	
Opioids		1.61 ² (-1.10, 4.27)	1.45 ³ (-6.89, 9.64)

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

Sleep quality, network estimate WMD (95% CrI)			
Covariate, length of follow-up		Placebo	Cannabis for medical use
Adjusted model		Unadjusted model	
		Placebo	5.95 (1.82, 10.24)
		Cannabis for medical use	-0.49 (-5.59, 4.72)
Covariate, sample size		Opioids	5.46 (2.62, 8.59)
		Placebo	8.74¹ (-1.97, 19.32)
		Cannabis for medical use	0.28 ³ (-12.32, 13.04)
Adjusted model		Opioids	9.10² (1.91, 16.26)
		Placebo	5.95 (1.82, 10.24)
		Cannabis for medical use	-0.49 (-5.59, 4.72)
Opioids		Opioids	5.46 (2.62, 8.59)
		Placebo	7.40¹ (0.75, 14.02)
		Cannabis for medical use	1.16 ³ (-6.58, 9.00)
		Opioids	8.56² (4.41, 12.75)

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

Discontinuations due to adverse events (enriched trials)			
Results are not reliable due to small number of studies. Number of studies for cannabis for medical use versus placebo = 2.			
Discontinuations due to adverse events (non-enriched trials), network estimate OR (95% CrI)			
Covariate, length of follow-up		Placebo	Cannabis for medical use
Adjusted model		Unadjusted model	
		Placebo	1.80 (1.19, 2.63)
		Cannabis for medical use	3.27 (2.71, 3.90)
Covariate, sample size		Opioids	0.75¹ (0.27, 1.84)
		Placebo	1.81 (1.21, 2.81)
		Cannabis for medical use	2.05² (1.40, 2.95)
Adjusted model		Opioids	2.70³ (1.08, 8.13)
		Placebo	1.80 (1.19, 2.63)
		Cannabis for medical use	3.27 (2.71, 3.90)
Opioids		Opioids	0.79¹ (0.32, 1.83)
		Placebo	1.81 (1.21, 2.81)
		Cannabis for medical use	2.87² (2.15, 3.79)
		Opioids	3.65³ (1.54, 9.22)

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use.

eTable 11. Network meta-analysis results for pain outcome by MME thresholds

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
-0.61 (-0.90, -0.32)	-0.31 (-0.73, 0.11)			
-0.92 (-1.23, -0.62)	-0.20 (-0.56, 0.17)	0.11 (-0.27, 0.49)		
-0.81 (-1.04, -0.58)	-0.20 (-0.58, 0.19)	0.11 (-0.28, 0.51)	0.00 (-0.34, 0.34)	
-0.81 (-1.06, -0.55)				Opioid MME 50 - 99mg

All values in bold are statistically significant at the 0.05 significance level

eTable 12. Network meta-analysis results for secondary outcomes by MME thresholds

Physical functioning

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
2.30 (0.35, 4.66)	-1.14 (-4.61, 1.88)			
1.14 (-1.28, 3.63)	-0.04 (-2.65, 2.59)	1.10 (-1.66, 4.36)		
2.25 (0.75, 4.26)	0.88 (-1.96, 3.56)	2.02 (-0.91, 5.28)	0.93 (-1.64, 3.29)	
3.17 (1.47, 5.23)				Opioid MME 50 - 99mg

All values in bold are statistically significant at the 0.05 significance level

Emotional functioning

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
0.66 (-1.01, 2.36)	-1.76 (-3.89, 0.44)			
-1.11 (-2.40, 0.34)	-0.59 (-2.75, 1.52)	1.17 (-0.83, 3.03)		
0.07 (-1.28, 1.42)	-1.93 (-3.87, 0.40)	-0.19 (-1.83, 1.96)	-1.36 (-2.96, 0.87)	
-1.29 (-2.35, 0.37)				Opioid MME 50 - 99mg

Role functioning

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
1.08 (-4.16, 6.90)	-3.77 (-12.25, 3.97)			
-2.70 (-8.69, 3.17)	1.72 (-5.28, 9.30)	5.47 (-1.54, 13.89)		
2.77 (-1.51, 8.36)	-0.61 (-8.18, 6.47)	3.19 (-4.34, 10.91)	-2.28 (-9.85, 3.98)	
0.48 (-4.29, 5.37)				Opioid MME 50 - 99mg

Social functioning

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
-1.33 (-5.06, 1.68)	-0.58 (-5.42, 4.77)			
-1.91 (-5.87, 1.82)				
-0.35 (-4.96, 4.41)	1.00 (-4.44, 7.11)	1.57 (-4.33, 7.76)		
1.93 (-1.13, 5.82)	3.26 (-0.97, 8.96)	3.84 (-0.81, 9.61)	2.30 (-3.22, 8.34)	

Sleep quality

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
5.93 (1.82, 10.24)				
0.09 (-11.56, 11.64)	-5.86 (-18.31, 6.37)			
4.39 (-0.12, 9.36)	-1.54 (-7.72, 4.88)	4.29 (-7.92, 17.09)		
9.56 (4.73, 14.56)	3.62 (-2.87, 10.08)	9.47 (-3.02, 22.16)	5.17 (-1.77, 11.81)	

All values in bold are statistically significant at the 0.05 significance level

Discontinuations due to adverse events (enriched trials)

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
0.99 (0.10, 10.65)				
1.23 (0.71, 2.18)	1.25 (0.11, 13.76)			
1.07 (0.63, 1.80)	1.07 (0.10, 11.38)	0.87 (0.40, 1.84)		
1.52 (0.80, 2.72)	1.52 (0.13, 16.32)	1.23 (0.53, 2.73)	1.42 (0.63, 3.12)	

Discontinuations due to adverse events (non-enriched trials)

Placebo	Cannabis for medical use	Opioid MME > 100 mg	Opioid MME < 50mg	Opioid MME 50 - 99mg
1.83 (1.19, 2.67)				
3.45 (2.12, 5.28)	1.88 (1.06, 3.44)			
2.92 (2.28, 3.88)	1.60 (1.01, 2.74)	0.85 (0.52, 1.51)		
4.02 (2.86, 5.31)	2.19 (1.36, 3.57)	1.17 (0.68, 1.98)	1.38 (0.86, 1.99)	

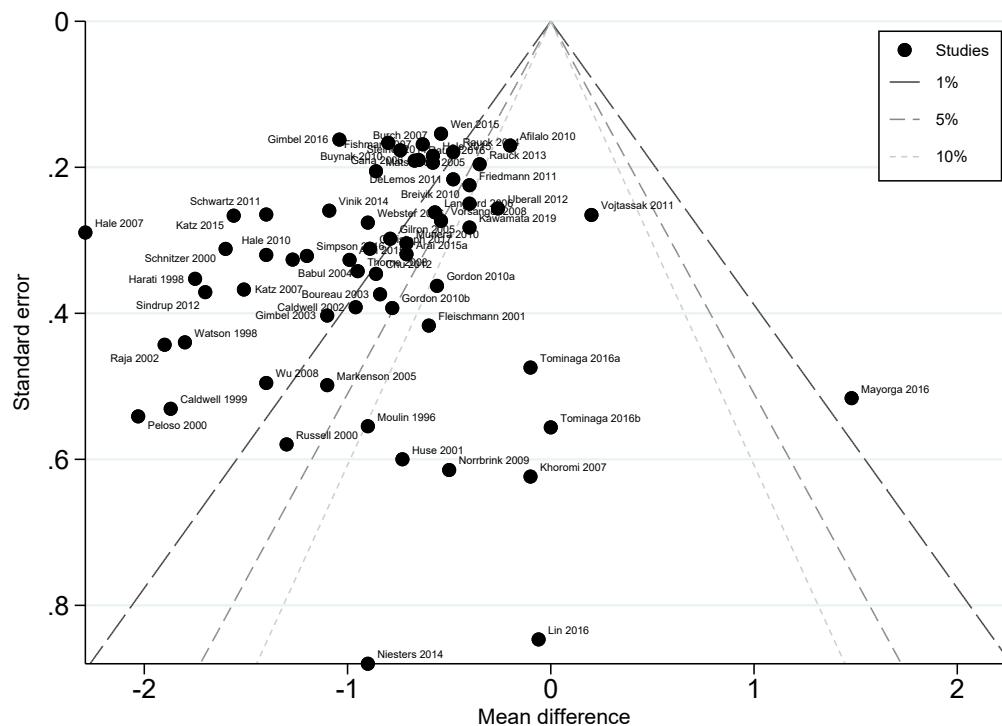
All values in bold are statistically significant at the 0.05 significance level

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5 **eTable 13. Pain studies from JAMA 2018 systematic review & meta-analysis included & excluded in network
6 meta-analysis**

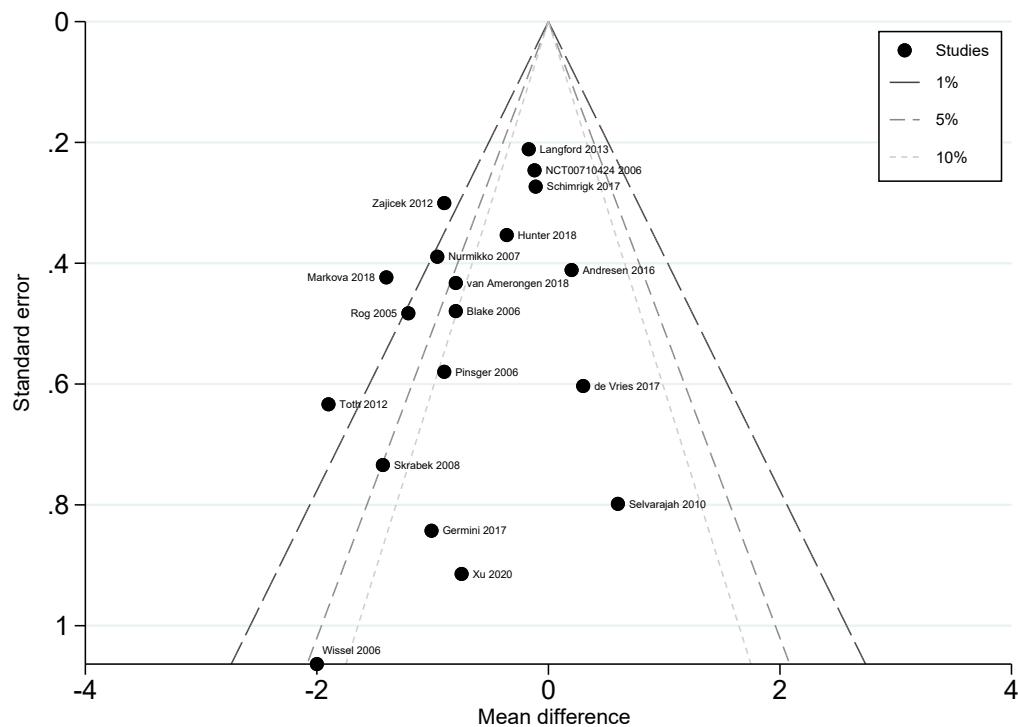
Author	Year	Inclusion or Exclusion reason	Author	Year	Inclusion or Exclusion reason
Fleischmann	2001	Included	Schwartz	2011	Included
Bennett	2003	Combination products	Steiner	2011	Included
Ruoff	2003	Combination products	Vojtassak	2011	Included
Babul	2004	Included	Rauck	2013	Included
Emkey	2004	Combination products	Rauck	2014	Included
Peloso	2004	Combination products	Vinik	2014	Included
Gana	2006	Included	Arai	2015	Included
Webster	2006	Included	Arai	2015	Included
Burch	2007	Included	Hale	2015	Included
Fishman	2007	Included	Katz	2015	Included
Hale	2007	Included	Rauck	2015	Combination products
Katz	2007	Included	Trenkwalder	2015	Combination products
Hanna	2008	Combination products	Wen	2015	Included
Vorsanger	2008	Included	Gimbel	2016	Included
Afilalo	2010	Included	Mayorga	2016	Included
Breivik	2010	Included	Rauck	2016	Included
Buynak	2010	Included	Simpson	2016	Included
Hale	2010	Included	Tominaga	2016	Included
Katz	2010	Combination products	Tominaga	2016	Included
DeLemos	2011	Included	Christoph	2017	Included
Friedmann	2011	Included	Serrie	2017	Incomplete reporting
Total number of studies 42; 9 exclusions; 33 inclusions					

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34 **eTable 14. Pain studies included in network meta-analysis excluded from pain JAMA 2018 systematic review
35 & meta-analysis**

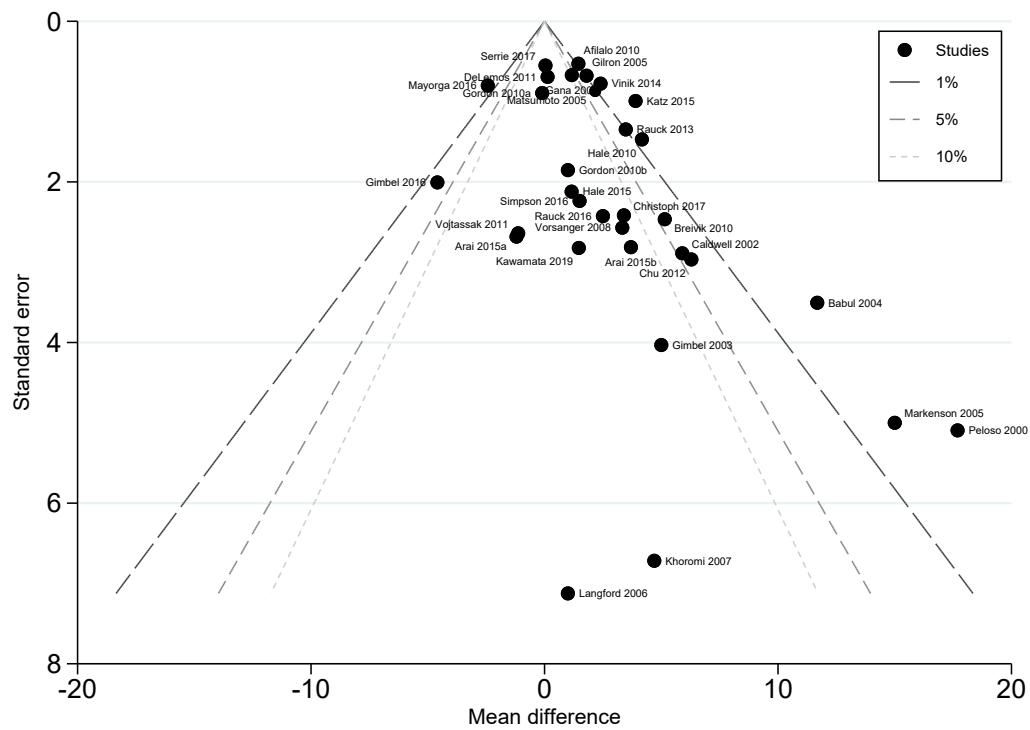
Author	Year	Exclusion reason from JAMA review	Author	Year	Exclusion reason from JAMA review
Moulin	1996	< 3months follow-up	Langford	2006	< 3months follow-up
Harati	1998	< 3months follow-up	Khoromi	2007	< 3months follow-up
Watson	1998	< 3months follow-up	Thorne	2008	< 3months follow-up
Caldwell	1999	< 3months follow-up	Wu	2008	Did not pass screening
Peloso	2000	< 3months follow-up	Norrbrink	2009	< 3months follow-up
Russell	2000	< 3months follow-up	Gordon	2010	< 3months follow-up
Schnitzer	2000	< 3months follow-up	Gordon	2010	< 3months follow-up
Huse	2001	< 3months follow-up	Munera	2010	< 3months follow-up
Caldwell	2002	< 3months follow-up	Chu	2012	< 3months follow-up
Raja	2002	< 3months follow-up	Sindrup	2012	< 3months follow-up
Boureau	2003	< 3months follow-up	Uberall	2012	< 3months follow-up
Gimbel	2003	< 3months follow-up	Niesters	2014	< 3months follow-up
Gilron	2005	< 3months follow-up	Lin	2016	< 3months follow-up
Markenson	2005	Did not pass screening	Kawamata	2019	Published after search execution end date
Matsumoto	2005	< 3months follow-up			
Total number of studies 29.					

eFigure 18. Funnel plot for pain for randomized trials of opioids versus placebo

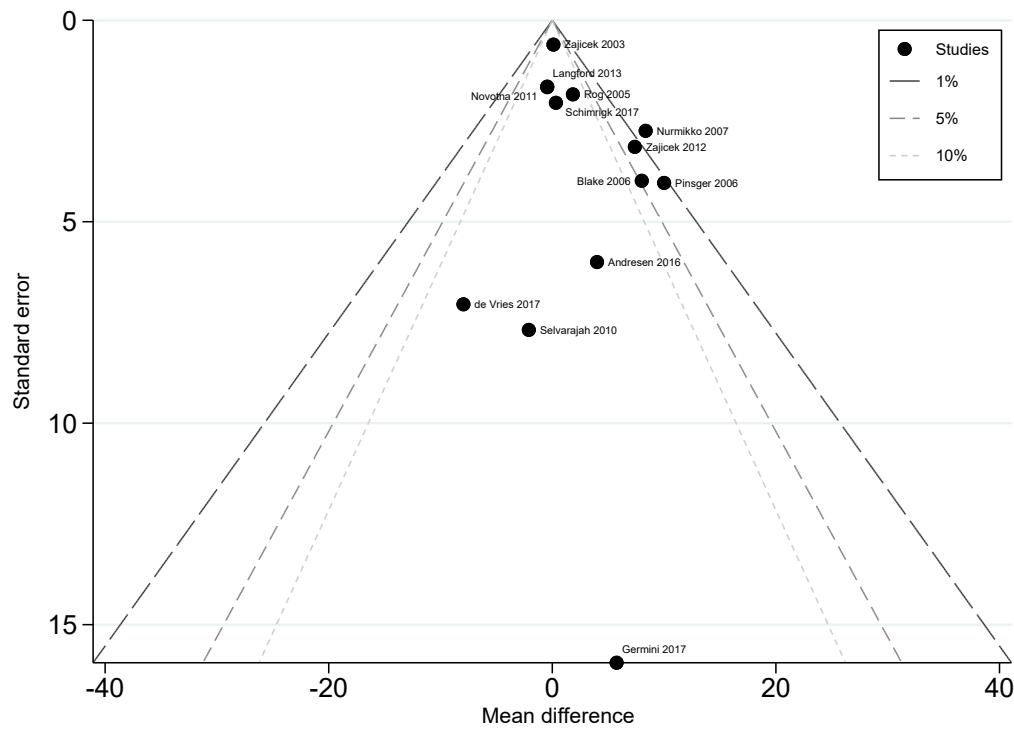
Egger's test p-value = 0.039

eFigure 19. Funnel plot for pain for randomized trials of cannabis for medical use versus placebo

Egger's test p-value = 0.044

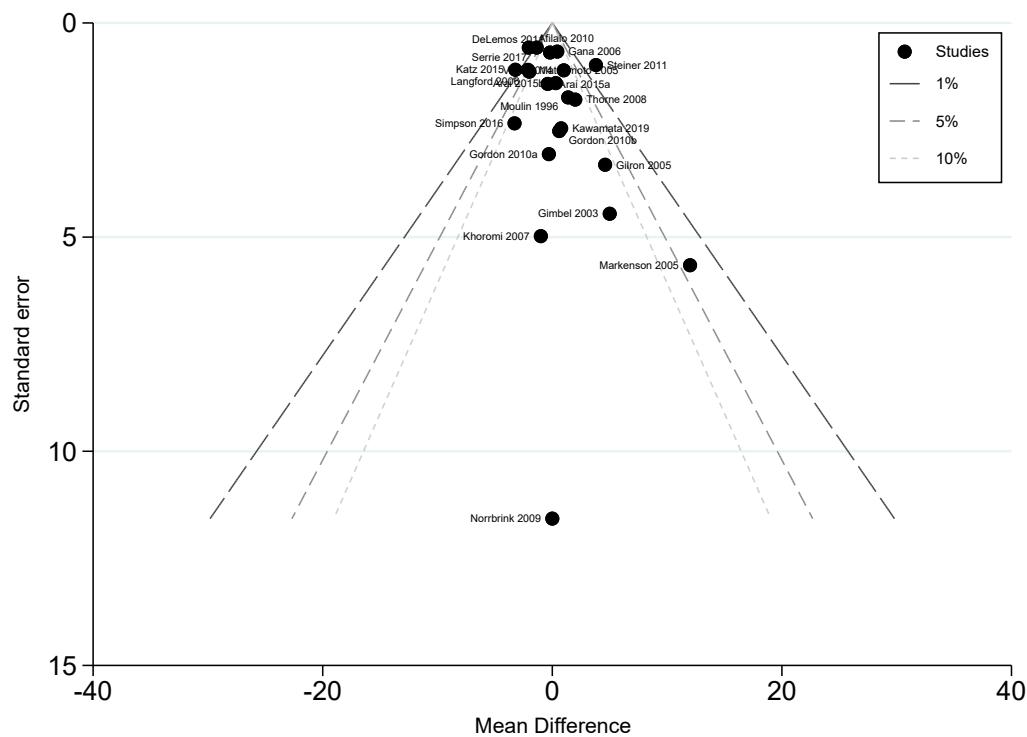
eFigure 20. Funnel plot for physical functioning for randomized trials of opioids versus placebo

Egger's test p-value = 0.015

eFigure 21. Funnel plot for physical functioning for randomized trials of cannabis for medical use versus placebo

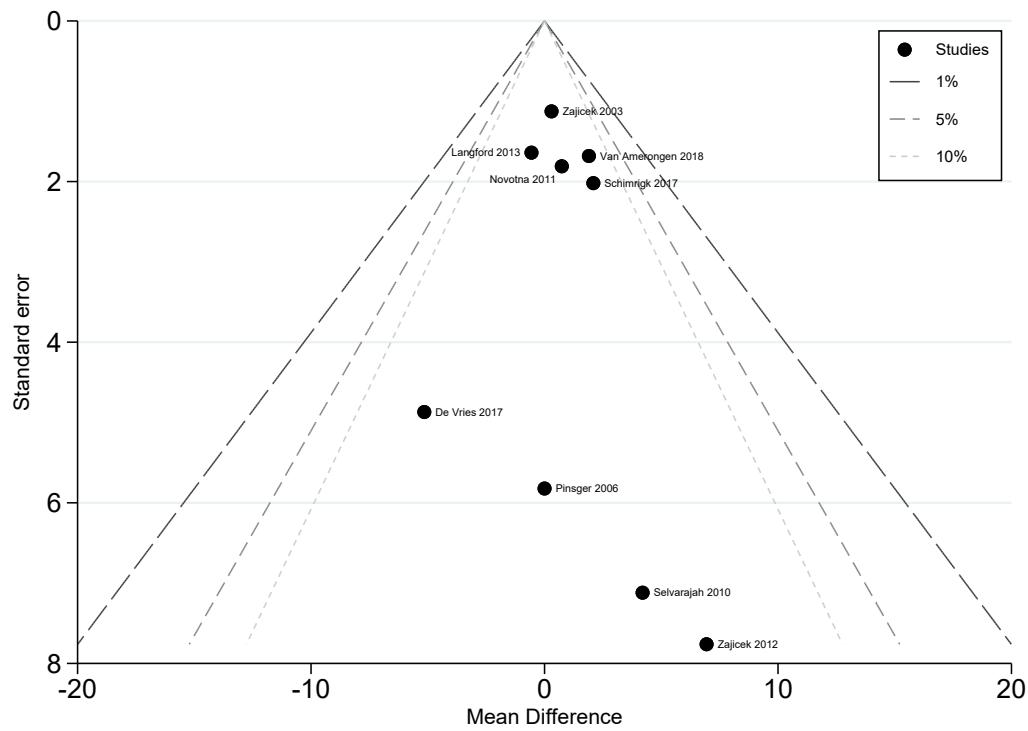
Egger's test p-value = 0.098

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5 **eFigure 22. Funnel plot for emotional functioning for randomized trials of opioids versus placebo**



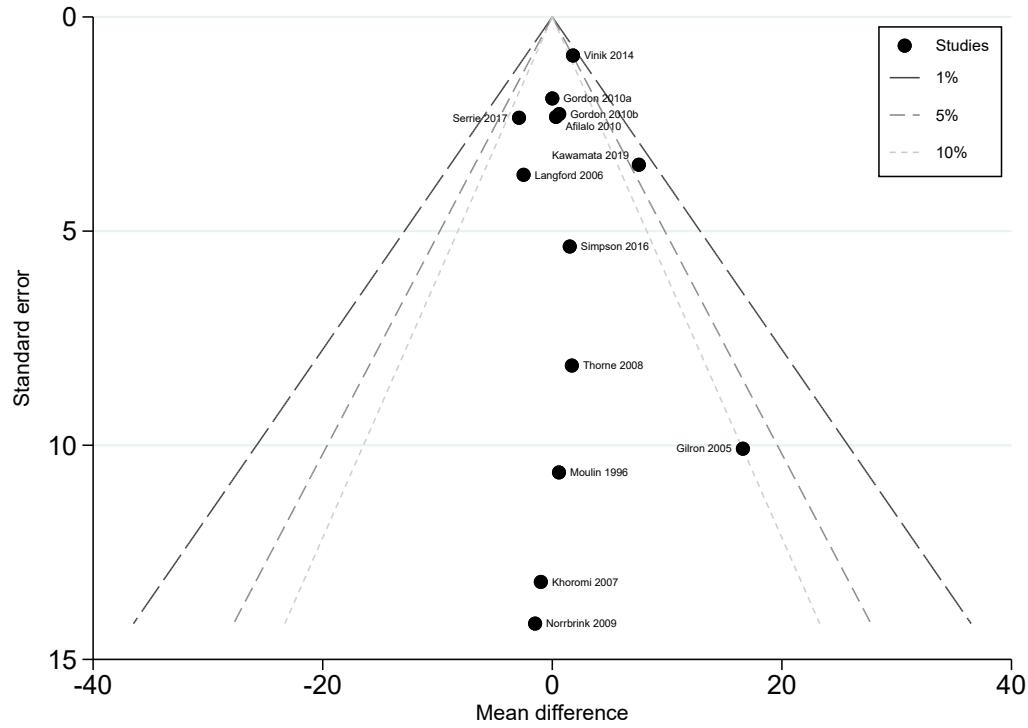
Egger's test p-value = 0.121

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 3 **eFigure 23. Funnel plot for emotional functioning for randomized trials of cannabis for medical use versus**
 4 **placebo**



Egger's test p-value = 0.71

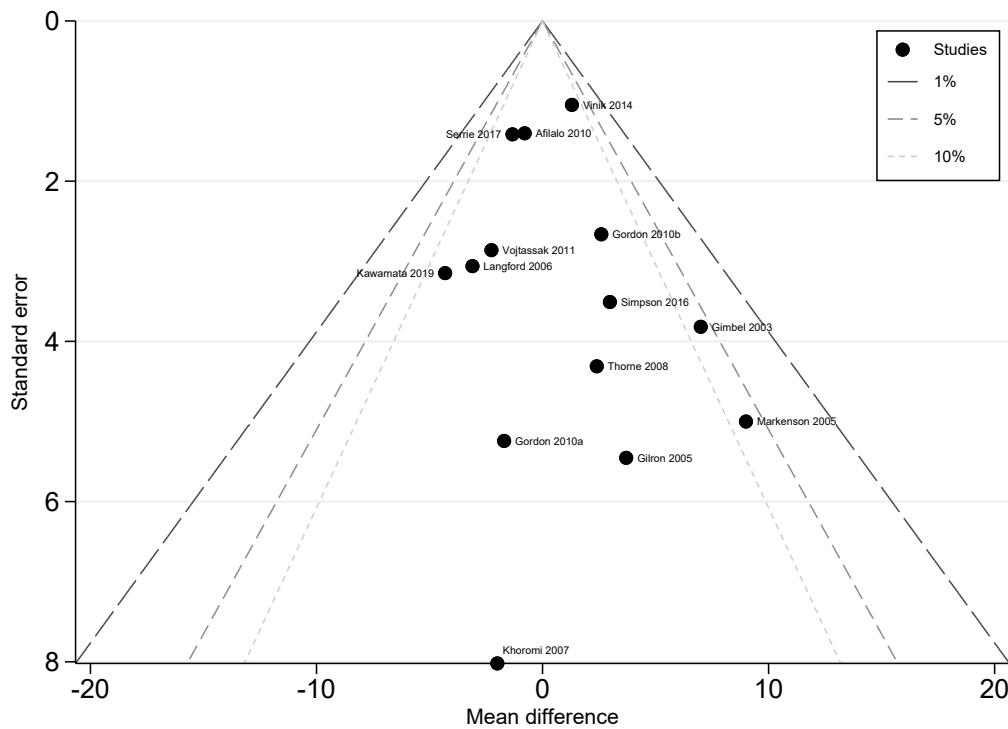
32 **eFigure 24. Funnel plot for role functioning for randomized trials of opioids versus placebo**



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3 Egger's test p-value = 0.967
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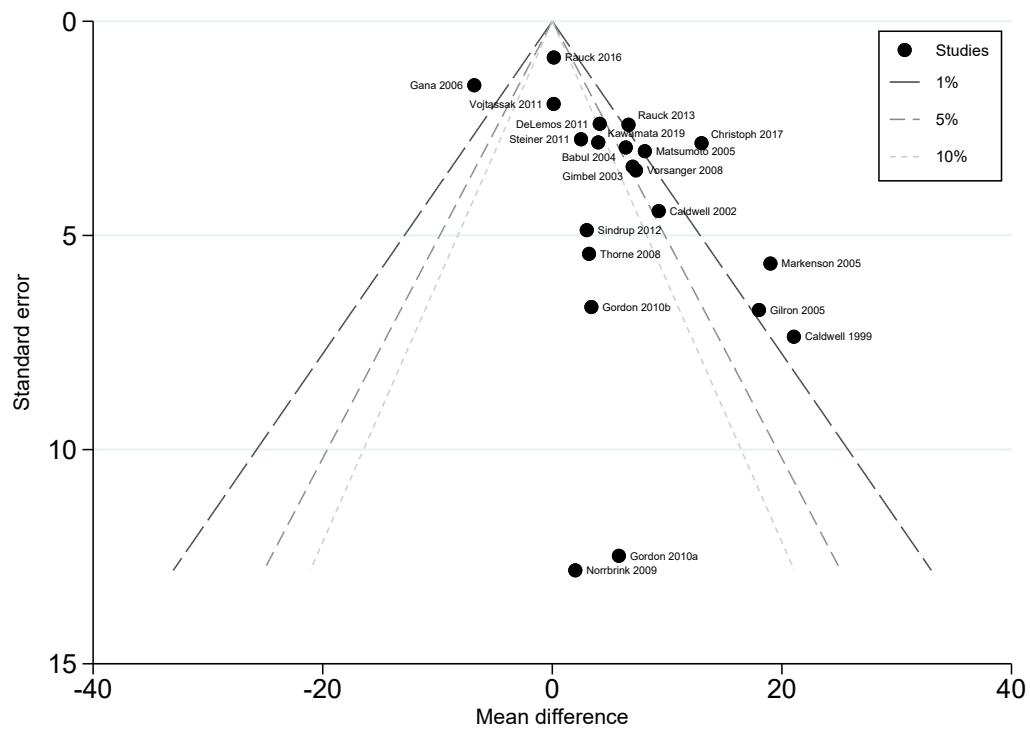
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eFigure 25. Funnel plot for social functioning for randomized trials of opioids versus placebo



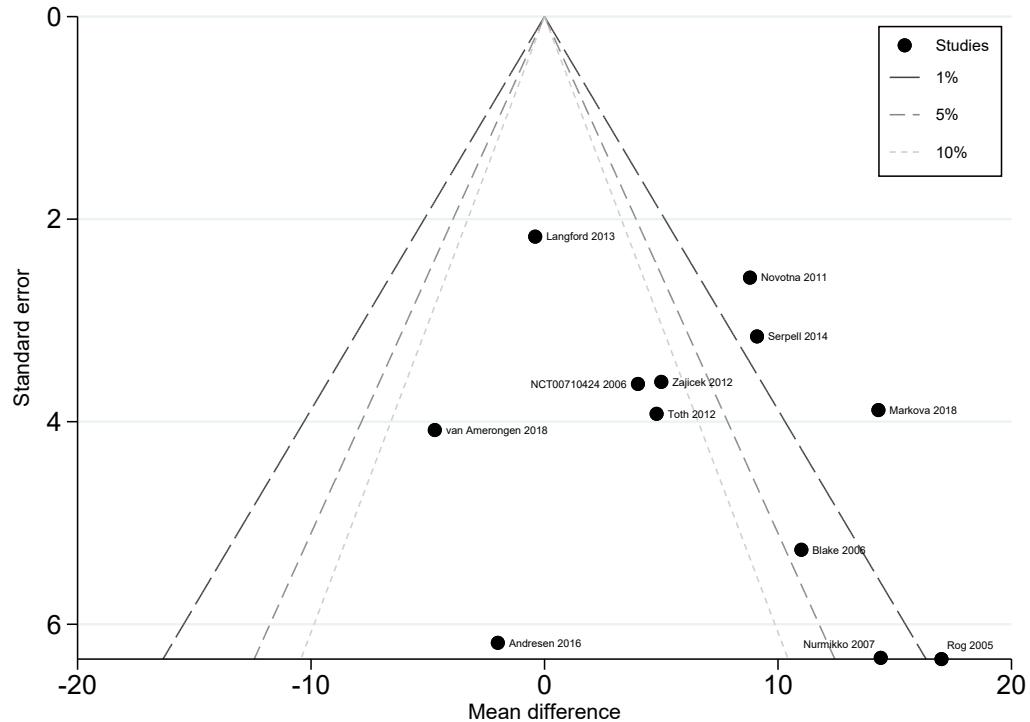
Egger's test p-value = 0.548

eFigure 26. Funnel plot for sleep quality for randomized trials of opioids versus placebo



Egger's test p-value = 0.003

eFigure 27. Funnel plot for sleep quality for randomized trials of cannabis for medical use versus placebo



Egger's test p-value = 0.258



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplement eAppendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7-8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 7-8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 7-8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 7-8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 7-8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7-9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8-9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). For peer review only - http://bmjopen.bmjjournals.org/site/about/guidelines.xhtml	Page 9



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 10
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 11 & Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1 & Supplement eAppendix 3
Study characteristics	17	Cite each included study and present its characteristics.	Supplement eTable 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplement eTable 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 10-13
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Table 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Table 3 & Supplement eTable 6-10; eFigure 19-27
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Table 3 & Supplement eTable 6-10; eFigure 19-27
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Table 3 & Supplement eTable 6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Table 2 & Supplement eTable 4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 18-19
	23b	Discuss any limitations of the evidence included in the review.	Page 20
	23c	Discuss any limitations of the review processes used.	Page 20



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	Page 20
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 10 & 23
Competing interests	26	Declare any competing interests of review authors.	Page 23
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 23

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
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